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(54) **NUCLEIC ACID AND AMINO ACID SEQUENCES FOR ATP-BINDING CASSETTE TRANSPORTER AND METHODS OF SCREENING FOR AGENTS THAT MODIFY ATP-BINDING CASSETTE TRANSPORTER**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 308 days.

This patent is subject to a terminal disclaimer.

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C12N 5/00	(2006.01)
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C12P 21/06	(2006.01)
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(58) **Field of Classification Search** 435/69.1, 435/325, 320.1, 455; 536/23.1, 23.5
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides nucleic acid and amino acid sequences of an ATP binding cassette transporter and mutated sequences thereof associated with macular degeneration. Methods of detecting agents that modify ATP-binding cassette transporter comprising combining purified ATP binding cassette transporter and at least one agent suspected of modifying the ATP binding cassette transporter an observing a change in at least one characteristic associated with ATP binding cassette transporter. Methods of detecting macular degeneration is also embodied by the present invention.

5 Claims, 19 Drawing Sheets

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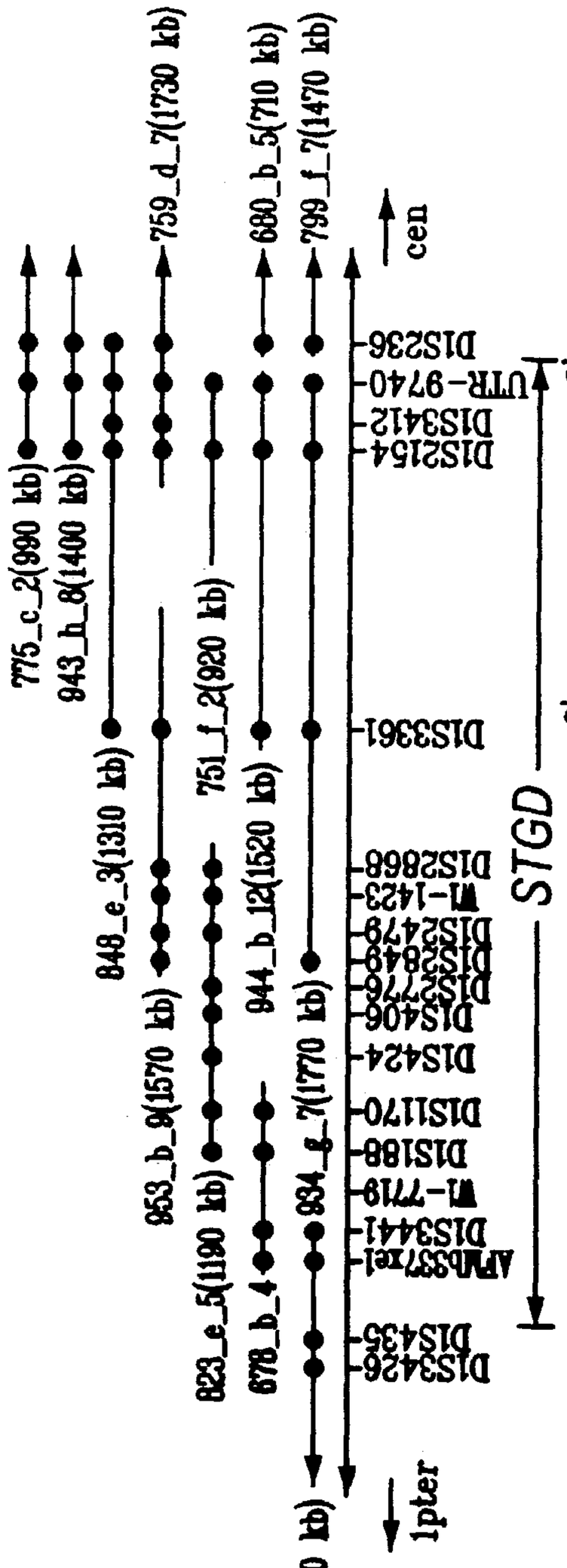
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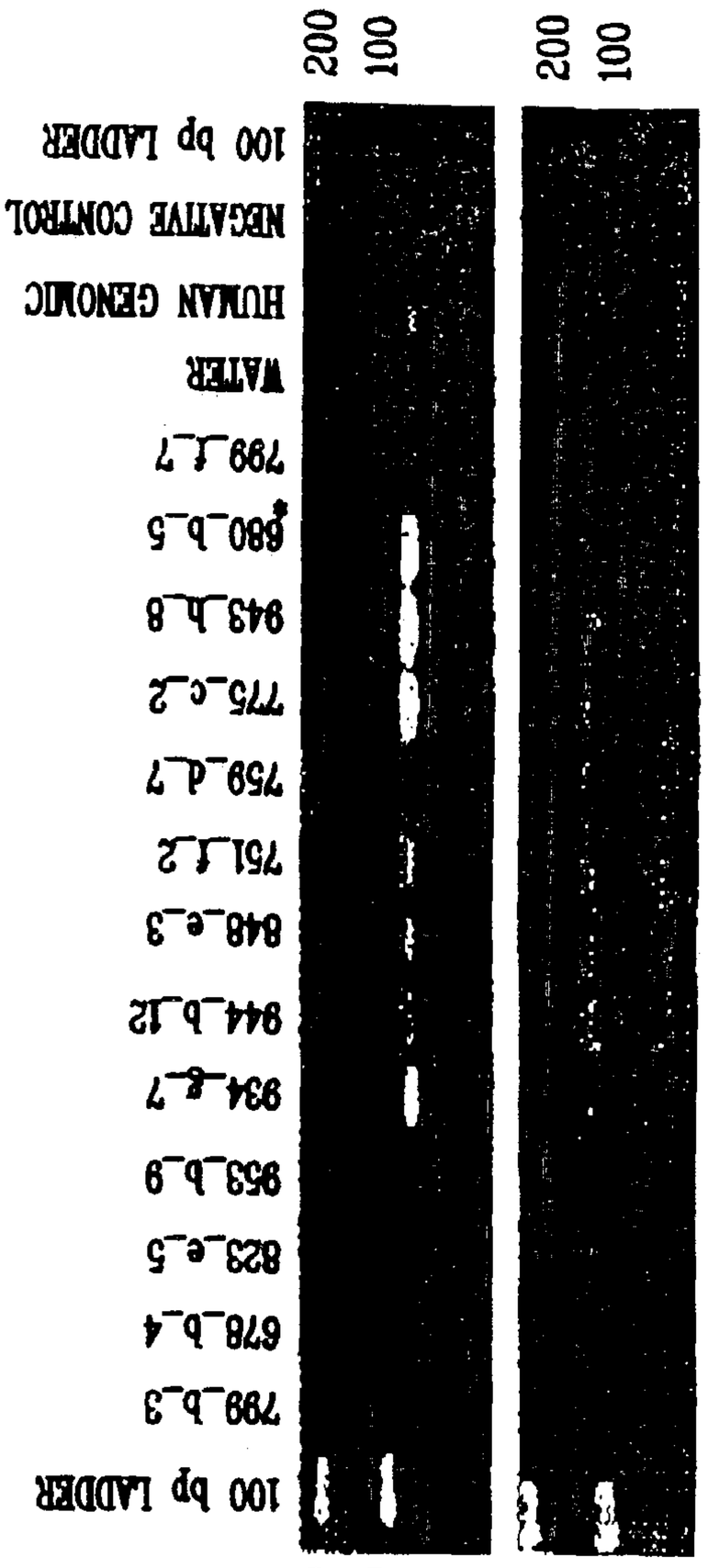
FIG. 1A


100 bp LADDER
NEGATIVE CONTROL
HUMAN GENOMIC
WATER
799_f_7
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775_c_2
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751_f_2
848_e_3
844_b_12
834_g_7
953_b_9
823_e_5
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799_b_3
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200
100
200
100
5' ABCR
3' ABCR

FIG. 1B

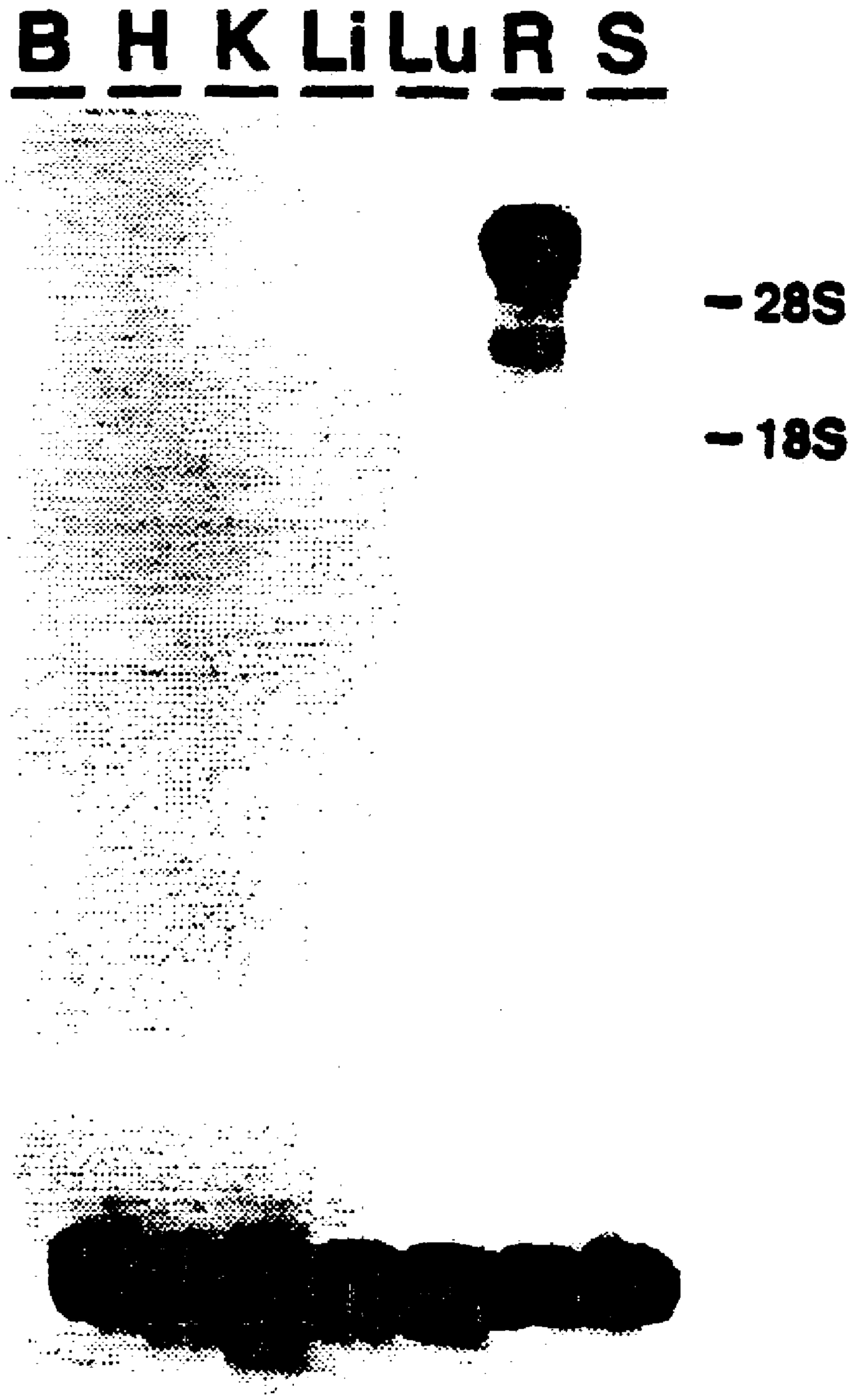

FIG. 2

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      -580                  -560                  -540
CCCCTACCCCTCTGCTAAGCTCAGGGATAACCCAACTAGCTGACCATAATGACTTCAGTC
      -520                  -500                  -480
ATTACGGAGCAAGATGAAAGACTAAAAGAGGGAGGGATCACTTCAGATCTGCCGAGTGAG
      -460                  -440                  -420
TCGATTGGACTTAAAGGGCCAGTCAAACCCTGACTGCCGGCTCATGGCAGGCTCTTGCCG
      -400                  -380                  -360
AGGACAAATGCCCAGCCTATATTTATGCAAAGAGATTTTGTTCCAAACTTAAGGTCAAAG
      -340                  -320                  -300
ATACCTAAAGACATCCCCCTCAGGAACCCCTCTCATGGAGGAGAGTGCCTGAGGGTCTTG
      -280                  -260                  -240
GTTTCCCATTGCATCCCCCACCTCAATTTCCCTGGTGCCCAGCCACTTGTGTCTTTAGGG
      -220                  -200                  -180
TTCTCTTTCTCTCCATAAAAGGGAGCCAACACAGTGTCGGCCTCCTCTCCCCAACTAAGG
      -160                  -140                  -120
GCTTATGTGTAATTAAAAGGGATTATGCTTTGAAGGGGAAAAGTAGCCTTTAATCACCAG
      -100                   -80                   -60
GAGAAGGACACAGCGTCCGGAGCCAGAGGCGCTCTTAACGGCGTTTATGTCCTTTGCTGT
       -40                   -20                     0
CCTGAGGGGCCTCAGCTCTGACCAATCTGGTCTTCGTGTGGTCATTAGCATGGGCTTCGT
                                                  M  G  F  V
        20                    40                    60
GAGACAGATACAGCTTTTGCTCTGGAAGAACTGGACCCTGCGGAAAAGGCAAAAGATTCG
 R  Q  I  Q  L  L  L  W  K  N  W  T  L  R  K  R  Q  K  I  R
        80                   100                   120
CTTTGTGGTGGAACTCGTGTGGCCTTTATCTTTATTTCTGGTCTTGATCTGGTTAAGGAA
 F  V  V  E  L  V  W  P  L  S  L  F  L  V  L  I  W  L  R  N
       140                   160                   180
TGCCAACCCGCTCTACAGCCATCATGAAT|GCCATTTCCCCAACAAGGCGATGCCCTCAGC
 A  N  P  L  Y  S  H  H  E  C     H  F  P  N  K  A  M  P  S  A
       200                   220                   240
AGGAATGCTGCCGTGGCTCCAGGGGATCTTCTGCAATGTGAACAATCCCTGTTTTCAAAG
 G  M  L  P  W  L  Q  G  I  F  C  N  V  N  N  P  C  F  Q  S
       260                   280                   300
CCCCACCCCAGGAGAATCTCCTGGAATTGTGTCAAACTATAACAACTCCAT|CTTGGCAAG
 P  T  P  G  E  S  P  G  I  V  S  N  Y  N  N  S  I     L  A  R
       320                   340                   360
GGTATATCGAGATTTTCAAGAACTCCTCATGAATGCACCAGAGAGCCAGCACCTTGGCCG
 V  Y  R  D  F  Q  E  L  L  M  N  A  P  E  S  Q  H  L  G  R
       380                   400                   420
TATTTGGACAGAGCTACACATCTTGTCCCAATTCATGGACACCCTCCGGACTCACCCGGA
 I  W  T  E  L  H  I  L  S  Q  F  M  D  T  L  R  T  H  P  E
       440                   460                   480
GAGAATTGCAG|GAAGAGGAATACGAATAAGGGATATCTTGAAAGATGAAGAAACACTGAC
 R  I  A  G     R  G  I  R  I  R  D  I  L  K  D  E  E  T  L  T
       500                   520                   540
ACTATTTCTCATTAAAAACATCGGCCTGTCTGACTCAGTGGTCTACCTTCTGATCAACTC
 L  F  L  I  K  N  I  G  L  S  D  S  V  V  Y  L  L  I  N  S
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FIG. 3A

```
       560                   580                   600
TCAAGTCCGTCCAGAGCAG|TTCGCTCATGGAGTCCCGGACCTGGCGCTGAAGGACATCGC
 Q  V  R  P  E  Q   F  A  H  G  V  P  D  L  A  L  K  D  I  A
       620                   640                   660
CTGCAGCGAGGCCCTCCTGGAGCGCTTCATCATCTTCAGCCAGAGACGCGGGGCAAAGAC
 C  S  E  A  L  L  E  R  F  I  I  F  S  Q  R  R  G  A  K  T
       680                   700                   720
GGTGCGCTATGCCCTGTGCTCCCTCTCCCAGGGCACCCTACAGTGGATAGAAGACACTCT
 V  R  Y  A  L  C  S  L  S  Q  G  T  L  Q  W  I  E  D  T  L
       740                   760                   780
GTATGCCAACGTGGACTTCTTCAAGCTCTTCCGTGTG|CTTCCCACACTCCTAGACAGCCG
 Y  A  N  V  D  F  F  K  L  F  R  V   L  P  T  L  L  D  S  R
       800                   820                   840
TTCTCAAGGTATCAATCTGAGATCTTGGGGAGGAATATTATCTGATATGTCACCAAGAAT
 S  Q  G  I  N  L  R  S  W  G  G  I  L  S  D  M  S  P  R  I
       860                   880                   900
TCAAGAG|TTTATCCATCGGCCGAGTATGCAGGACTTGCTGTGGGTGACCAGGCCCCTCAT
 Q  E   F  I  H  R  P  S  M  Q  D  L  L  W  V  T  R  P  L  M
       920                   940                   960
GCAGAATGGTGGTCCAGAGACCTTTACAAAGCTGATGGGCATCCTGTCTGACCTCCTGTG
 Q  N  G  G  P  E  T  F  T  K  L  M  G  I  L  S  D  L  L  C
       980                  1000                  1020
TGGCTACCCCGAGGGAGGTGGCTCTCGGGTGCTCTCCTTCAACTGGTATGAAGACAATAA
 G  Y  P  E  G  G  G  S  R  V  L  S  F  N  W  Y  E  D  N  N
      1040                  1060                  1080
CTATAAGGCCTTTCTGGGGATTGACTCCACAAGGAAGGATCCTATCTATTCTTATGACAG
 Y  K  A  F  L  G  I  D  S  T  R  K  D  P  I  Y  S  Y  D  R
      1100                  1120                  1140
AAGAACAA|CATCCTTTTGTAATGCATTGATCCAGAGCCTGGAGTCAAATCCTTTAACCAA
 R  T  T   S  F  C  N  A  L  I  Q  S  L  E  S  N  P  L  T  K
      1160                  1180                  1200
AATCGCTTGGAGGGCGGCAAAGCCTTTGCTGATGGGAAAAATCCTGTACACTCCTGATTC
 I  A  W  R  A  A  K  P  L  L  M  G  K  I  L  Y  T  P  D  S
      1220                  1240                  1260
ACCTGCAGCACGAAGGATACTGAAGAAT|GCCAACTCAACTTTTGAAGAACTGGAACACGT
 P  A  A  R  R  I  L  K  N   A  N  S  T  F  E  E  L  E  H  V
      1280                  1300                  1320
TAGGAAGTTGGTCAAAGCCTGGGAAGAAGTAGGGCCCCAGATCTGGTACTTCTTTGACAA
 R  K  L  V  K  A  W  E  E  V  G  P  Q  I  W  Y  F  F  D  N
      1340                  1360                  1380
CAGCACACAGATGAACATGATCAGA|GATACCCTGGGGAACCCAACAGTAAAAGACTTTTT
 S  T  Q  M  N  M  I  R   D  T  L  G  N  P  T  V  K  D  F  L
      1400                  1420                  1440
GAATAGGCAGCTTGGTGAAGAAGGTATTACTGCTGAAGCCATCCTAAACTTCCTCTACAA
 N  R  Q  L  G  E  E  G  I  T  A  E  A  I  L  N  F  L  Y  K
      1460                  1480                  1500
GGGCCCTCGGGAAAGCCAGGCTGACGACATGGCCAACTTCGACTGGAGGGACATATTTAA
 G  P  R  E  S  Q  A  D  D  M  A  N  F  D  W  R  D  I  F  N
      1520                  1540                  1560
CATCACTGATCGCACCCTCCGCCTGGTCAATCAATACCTGGAG|TGCTTGGTCCTGGATAA
 I  T  D  R  T  L  R  L  V  N  Q  Y  L  E   C  L  V  L  D  K
```

FIG. 3B

```
      1580                  1600                  1620
GTTTGAAAGCTACAATGATGAAACTCAGCTCACCCAACGTGCCCTCTCTCTACTGGAGGA
 F  E  S  Y  N  D  E  T  Q  L  T  Q  R  A  L  S  L  L  E  E
      1640                  1660                  1680
AAACATGTTCTGGGCCGGAGTGGTATTCCCTGACATGTATCCCTGGACCAGCTCTCTACC
 N  M  F  W  A  G  V  V  F  P  D  M  Y  P  W  T  S  S  L  P
      1700                  1720                  1740
ACCCCACGTGAAGTATAAGATCCGAATGGACATAGACGTGGTGGAGAAAACCAATAAGAT
 P  H  V  K  Y  K  I  R  M  D  I  D  V  V  E  K  T  N  K  I
      1760                  1780                  1800
TAAAGACAG|GTATTGGGATTCTGGTCCCAGAGCTGATCCCGTGGAAGATTTCCGGTACAT
 K  D  R   Y  W  D  S  G  P  R  A  D  P  V  E  D  F  R  Y  I
      1820                  1840                  1860
CTGGGGCGGGTTTGCCTATCTGCAGGACATGGTTGAACAGGGGATCACAAGGAGCCAGGT
 W  G  G  F  A  Y  L  Q  D  M  V  E  Q  G  I  T  R  S  Q  V
      1880                  1900                  1920
GCAGGCGGAGGCTCCAGTTGGAATCTACCTCCAGCAGATGCCCTACCCCTGCTTCGTGGA
 Q  A  E  A  P  V  G  I  Y  L  Q  Q  M  P  Y  P  C  F  V  D
      1940                  1960                  1980
CGATTC|TTTCATGATCATCCTGAACCGCTGTTTCCCTATCTTCATGGTGCTGGCATGGAT
 D  S   F  M  I  I  L  N  R  C  F  P  I  F  M  V  L  A  W  I
      2000                  2020                  2040
CTACTCTGTCTCCATGACTGTGAAGAGCATCGTCTTGGAGAAGGAGTTGCGACTGAAGGA
 Y  S  V  S  M  T  V  K  S  I  V  L  E  K  E  L  R  L  K  E
      2060                  2080                  2100
GACCTTGAAAAATCAGGGTGTCTCCAATGCAGTGATTTGGTGTACCTGGTTCCTGGACAG
 T  L  K  N  Q  G  V  S  N  A  V  I  W  C  T  W  F  L  D  S
      2120                  2140                  2160
CTTCTCCATCATGTCGATGAGCATCTTCCTCCTGACGATATTCATCATGCATG|GAAGAAT
 F  S  I  M  S  M  S  I  F  L  L  T  I  F  I  M  H  G   R  I
      2180                  2200                  2220
CCTACATTACAGCGACCCATTCATCCTCTTCCTGTTCTTGTTGGCTTTCTCCACTGCCAC
 L  H  Y  S  D  P  F  I  L  F  L  F  L  L  A  F  S  T  A  T
      2240                  2260                  2280
CATCATGCTGTGCTTTCTGCTCAGCACCTTCTTCTCCAAGGCCAGTCTGGCAGCAGCCTG
 I  M  L  C  F  L  L  S  T  F  F  S  K  A  S  L  A  A  A  C
      2300                  2320                  2340
TAGTGGTGTCATCTATTTCACCCTCTACCTGCCACACATCCTGTGCTTCGCCTGGCAGGA
 S  G  V  I  Y  F  T  L  Y  L  P  H  I  L  C  F  A  W  Q  D
      2360                  2380                  2400
CCGCATGACCGCTGAGCTGAAGAAGGCTGTG|AGCTTACTGTCTCCGGTGGCATTTGGATT
 R  M  T  A  E  L  K  K  A  V   S  L  L  S  P  V  A  F  G  F
      2420                  2440                  2460
TGGCACTGAGTACCTGGTTCGCTTTGAAGAGCAAGGCCTGGGGCTGCAGTGGAGCAACAT
 G  T  E  Y  L  V  R  F  E  E  Q  G  L  G  L  Q  W  S  N  I
      2480                  2500                  2520
CGGGAACAGTCCCACGGAAGGGGACGAATTCAGCTTCCTGCTGTCCATGCAGATGATGCT
 G  N  S  P  T  E  G  D  E  F  S  F  L  L  S  M  Q  M  M  L
      2540                  2560                  2580
CCTTGATGCTGCGTGCTATGGCTTACTCGCTTGGTACCTTGATCAGGTGTTTCCAG|GAGA
 L  D  A  A  C  Y  G  L  L  A  W  Y  L  D  Q  V  F  P  G   D
```

FIG. 3C

```
      2600                  2620                  2640
CTATGGAACCCCACTTCCTTGGTACTTTCTTCTACAAGAGTCGTATTGGCTTAGCGGTGA
 Y  G  T  P  L  P  W  Y  F  L  L  Q  E  S  Y  W  L  S  G  E
      2660                  2680                  2700
AG|GGTGTTCAACCAGAGAAGAAAGAGCCCTGGAAAAGACCGAGCCCCTAACAGAGGAAAC
 G   C  S  T  R  E  E  R  A  L  E  K  T  E  P  L  T  E  E  T
      2720                  2740                  2760
GGAGGATCCAGAGCACCCAGAAGGAATACACG|ACTCCTTCTTTGAACGTGAGCATCCAGG
 E  D  P  E  H  P  E  G  I  H  D   S  F  F  E  R  E  H  P  G
      2780                  2800                  2820
GTGGGTTCCTGGGGTATGCGTGAAGAATCTGGTAAAGATTTTTGAGCCCTGTGGCCGGCC
 W  V  P  G  V  C  V  K  N  L  V  K  I  F  E  P  C  G  R  P
      2840                  2860                  2880
AGCTGTGGACCGTCTGAACATCACCTTCTACGAGAACCAGATCACCGCATTCCTGGGCCA
 A  V  D  R  L  N  I  T  F  Y  E  N  Q  I  T  A  F  L  G  H
      2900                  2920                  2940
CAATGGAGCTGGGAAAACCACCACCTT|GTCCATCCTGACGGGTCTGTTGCCACCAACCTC
 N  G  A  G  K  T  T  T  L   S  I  L  T  G  L  L  P  P  T  S
      2960                  2980                  3000
TGGGACTGTGCTCGTTGGGGGAAGGGACATTGAAACCAGCCTGGATGCAGTCCGGCAGAG
 G  T  V  L  V  G  G  R  D  I  E  T  S  L  D  A  V  R  Q  S
      3020                  3040                  3060
CCTTGGCATGTGTCCACAGCACAACATCCTGTTCCACCA|CCTCACGGTGGCTGAGCACAT
 L  G  M  C  P  Q  H  N  I  L  F  H  H   L  T  V  A  E  H  M
      3080                  3100                  3120
GCTGTTCTATGCCCAGCTGAAAGGAAAGTCCCAGGAGGAGGCCCAGCTGGAGATGGAAGC
 L  F  Y  A  Q  L  K  G  K  S  Q  E  E  A  Q  L  E  M  E  A
      3140                  3160                  3180
CATGTTGGAGGACACAGGCCTCCACCACAAGCGGAATGAAGAGGCTCAGGACCTATCAG|G
 M  L  E  D  T  G  L  H  H  K  R  N  E  E  A  Q  D  L  S  G
      3200                  3220                  3240
TGGCATGCAGAGAAAGCTGTCGGTTGCCATTGCCTTTGTGGGAGATGCCAAGGTGGTGAT
 G  M  Q  R  K  L  S  V  A  I  A  F  V  G  D  A  K  V  V  I
      3260                  3280                  3300
TCTGGACGAACCCACCTCTGGGGTGGACCCTTACTCGAGACGCTCAATCTGGGATCTGCT
 L  D  E  P  T  S  G  V  D  P  Y  S  R  R  S  I  W  D  L  L
      3320                  3340                  3360
CCTGAAGTATCGCTCAG|GCAGAACCATCATCATGCCCACTCACCACATGGACGAGGCCGA
 L  K  Y  R  S  G   R  T  I  I  M  P  T  H  H  M  D  E  A  D
      3380                  3400                  3420
CCACCAAGGGGACCGCATTGCCATCATTGCCCAGGGAAGGCTCTACTGCTCAGGCACCCC
 H  Q  G  D  R  I  A  I  I  A  Q  G  R  L  Y  C  S  G  T  P
      3440                  3460                  3480
ACTCTTCCTGAAGAACTGCTTTGGCACAGGCTTGTACTTAACCTTGGTGCGCAAGATGAA
 L  F  L  K  N  C  F  G  T  G  L  Y  L  T  L  V  R  K  M  K
      3500                  3520                  3540
AAACATCCAGAGCCAAAGGAAAGGCAGTGAG|GGGACCTGCAGCTGCTCGTCTAAGGGTTT
 N  I  Q  S  Q  R  K  G  S  E   G  T  C  S  C  S  S  K  G  F
      3560                  3580                  3600
CTCCACCACGTGTCCAGCCCACGTCGATGACCTAACTCCAGAACAAGTCCTGGATGGGGA
 S  T  T  C  P  A  H  V  D  D  L  T  P  E  Q  V  L  D  G  D
```

FIG. 3D

```
      3620                3640                3660
TGTAAATGAGCTGATGGATGTAGTTCTCCACCATGTTCCAGAGGCAAAGCTGGTGGAGTG
 V  N  E  L  M  D  V  V  L  H  H  V  P  E  A  K  L  V  E  C
      3680                3700                3720
CATTGGTCAAGAACTTATCTTCCTTCTTCCAAATAAGAACTTCAAGCACAGAGCATATGC
 I  G  Q  E  L  I  F  L  L  P  N  K  N  F  K  H  R  A  Y  A
      3740                3760                3780
CAGCCTTTTCAGAGAGCTGGAGGAGACGCTGGCTGACCTTGGTCTCAGCAGTTTTGGAAT
 S  L  F  R  E  L  E  E  T  L  A  D  L  G  L  S  S  F  G  I
      3800                3820                3840
TTCTGACACTCCCCTGGAAGAG|ATTTTTCTGAAGGTCACGGAGGATTCTGATTCAGGACC
 S  D  T  P  L  E  E   I  F  L  K  V  T  E  D  S  D  S  G  P
      3860                3880                3900
TCTGTTTGCGG|GTGGCGCTCAGCAGAAAAGAGAAAACGTCAACCCCCGACACCCCTGCTT
 L  F  A  G   G  A  Q  Q  K  R  E  N  V  N  P  R  H  P  C  L
      3920                3940                3960
GGGTCCCAGAGAGAAGGCTGGACAGACACCCCAGGACTCCAATGTCTGCTCCCCAGGGGC
 G  P  R  E  K  A  G  Q  T  P  Q  D  S  N  V  C  S  P  G  A
      3980                4000                4020
GCCGGCTGCTCACCCAGAGGGCCAGCCTCCCCCAGAGCCAGAGTGCCCAGGCCCGCAGCT
 P  A  A  H  P  E  G  Q  P  P  P  E  P  E  C  P  G  P  Q  L
      4040                4060                4080
CAACACGGGGACACAGCTGGTCCTCCAGCATGTGCAGGCGCTGCTGGTCAAGAGATTCCA
 N  T  G  T  Q  L  V  L  Q  H  V  Q  A  L  L  V  K  R  F  Q
      4100                4120                4140
ACACACCATCCGCAGCCACAAGGACTTCCTGGCGCAG|ATCGTGCTCCCGGCTACCTTTGT
 H  T  I  R  S  H  K  D  F  L  A  Q   I  V  L  P  A  T  F  V
      4160                4180                4200
GTTTTTGGCTCTGATGCTTTCTATTGTTATCCTTCCTTTTGGCGAATACCCCGCTTTGAC
 F  L  A  L  M  L  S  I  V  I  L  P  F  G  E  Y  P  A  L  T
      4220                4240                4260
CCTTCACCCCTGGATATATGGGCAGCAGTACACCTTCTTCAG|CATGGATGAACCAGGCAG
 L  H  P  W  I  Y  G  Q  Q  Y  T  F  F  S   M  D  E  P  G  S
      4280                4300                4320
TGAGCAGTTCACGGTACTTGCAGACGTCCTCCTGAATAAGCCAGGCTTTGGCAACCGCTG
 E  Q  F  T  V  L  A  D  V  L  L  N  K  P  G  F  G  N  R  C
      4340                4360                4380
CCTGAAGGAAGGGTGGCTTCC|GGAGTACCCCTGTGGCAACTCAACACCCTGGAAGACTCC
 L  K  E  G  W  L  P   E  Y  P  C  G  N  S  T  P  W  K  T  P
      4400                4420                4440
TTCTGTGTCCCCAAACATCACCCAGCTGTTCCAGAAGCAGAAATGGACACAGGTCAACCC
 S  V  S  P  N  I  T  Q  L  F  Q  K  Q  K  W  T  Q  V  N  P
      4460                4480                4500
TTCACCATCCTGCAG|GTGCAGCACCAGGGAGAAGCTCACCATGCTGCCAGAGTGCCCCGA
 S  P  S  C  R   C  S  T  R  E  K  L  T  M  L  P  E  C  P  E
      4520                4540                4560
GGGTGCCGGGGGCCTCCCGCCCCCCCAG|AGAACACAGCGCAGCACGGAAATTCTACAAGA
 G  A  G  G  L  P  P  P  Q   R  T  Q  R  S  T  E  I  L  Q  D
```

FIG. 3E

```
      4580                4600                4620
CCTGACGGACAGGAACATCTCCGACTTCTTGGTAAAAACGTATCCTGCTCTTATAAGAAG
 L  T  D  R  N  I  S  D  F  L  V  K  T  Y  P  A  L  I  R  S
      4640                4660                4680
CAGC|TTAAAGAGCAAATTCTGGGTCAATGAACAGAG|GTATGGAGGAATTTCCATTGGAGG
 S   L  K  S  K  F  W  V  N  E  Q  R   Y  G  G  I  S  I  G  G
      4700                4720                4740
AAAGCTCCCAGTCGTCCCCATCACGGGGGAAGCACTTGTTGGGTTTTTAAGCGACCTTGG
 K  L  P  V  V  P  I  T  G  E  A  L  V  G  F  L  S  D  L  G
      4760                4780                4800
CCGGATCATGAATGTGAGCGGG|GGCCCTATCACTAGAGAGGCCTCTAAAGAAATACCTGA
 R  I  M  N  V  S  G   G  P  I  T  R  E  A  S  K  E  I  P  D
      4820                4840                4860
TTTCCTTAAACATCTAGAAACTGAAGACAACATTA|AGGTGTGGTTTAATAACAAAGGCTG
 F  L  K  H  L  E  T  E  D  N  I  K   V  W  F  N  N  K  G  W
      4880                4900                4920
GCATGCCCTGGTCAGCTTTCTCAATGTGGCCCACAACGCCATCTTACGGGCCAGCCTGCC
 H  A  L  V  S  F  L  N  V  A  H  N  A  I  L  R  A  S  L  P
      4940                4960                4980
TAAGGACAGGAGCCCCGAGGAGTATGGAATCACCGTCATTAGCCAACCCCTGAACCTGAC
 K  D  R  S  P  E  E  Y  G  I  T  V  I  S  Q  P  L  N  L  T
      5000                5020                5040
CAAGGAGCAGCTCTCAGAGATTACAGT|GCTGACCACTTCAGTGGATGCTGTGGTTGCCAT
 K  E  Q  L  S  E  I  T  V   L  T  T  S  V  D  A  V  V  A  I
      5060                5080                5100
CTGCGTGATTTTCTCCATGTCCTTCGTCCCAGCCAGCTTTGTCCTTTATTTGATCCAGGA
 C  V  I  F  S  M  S  F  V  P  A  S  F  V  L  Y  L  I  Q  E
      5120                5140                5160
GCGGGTGAACAAATCCAAGCACCTCCAGTTTATCAGTGGAGTGAGCCCCACCACCTACTG
 R  V  N  K  S  K  H  L  Q  F  I  S  G  V  S  P  T  T  Y  W
      5180                5200                5220
GGTGACCAACTTCCTCTGGGACATC|ATGAATTATTCCGTGAGTGCTGGGCTGGTGGTGGG
 V  T  N  F  L  W  D  I   M  N  Y  S  V  S  A  G  L  V  V  G
      5240                5260                5280
CATCTTCATCGGGTTTCAGAAGAAAGCCTACACTTCTCCAGAAAACCTTCCTGCCCTTGT
 I  F  I  G  F  Q  K  K  A  Y  T  S  P  E  N  L  P  A  L  V
      5300                5320                5340
GGCACTGCTCCTGCTGTATGG|ATGGGCGGTCATTCCCATGATGTACCCAGCATCCTTCCT
 A  L  L  L  L  Y  G   W  A  V  I  P  M  M  Y  P  A  S  F  L
      5360                5380                5400
GTTTGATGTCCCCAGCACAGCCTATGTGGCTTTATCTTGTGCTAATCTGTTCATCGGCAT
 F  D  V  P  S  T  A  Y  V  A  L  S  C  A  N  L  F  I  G  I
      5420                5440                5460
CAACAGCAGTGCTATTACCTTCATCTTGGAATTATTTGATAATAACCGG|ACGCTGCTCAG
 N  S  S  A  I  T  F  I  L  E  L  F  D  N  N  R   T  L  L  R
      5480                5500                5520
GTTCAACGCCGTGCTGAGGAAGCTGCTCATTGTCTTCCCCCACTTCTGCCTGGGCCGGGG
 F  N  A  V  L  R  K  L  L  I  V  F  P  H  F  C  L  G  R  G
```

FIG. 3F

```
      5540                5560                5580
CCTCATTGACCTTGCACTGAGCCAGGCTGTGACAGATGTCTATGCCCGGTTTG|GTGAGGA
 L  I  D  L  A  L  S  Q  A  V  T  D  V  Y  A  R  F  G   E  E
      5600                5620                5640
GCACTCTGCAAATCCGTTCCACTGGGACCTGATTGGGAAGAACCTGTTTGCCATGGTGGT
 H  S  A  N  P  F  H  W  D  L  I  G  K  N  L  F  A  M  V  V
      5660                5680                5700
GGAAGGGGTGGTGTACTTCCTCCTGACCCTGCTGGTCCAGCGCCACTTCTTCCTCTCCCA
 E  G  V  V  Y  F  L  L  T  L  L  V  Q  R  H  F  F  L  S  Q
      5720                5740                5760
ATG|GATTGCCGAGCCCACTAAGGAGCCCATTGTTGATGAAGATGATGATGTGGCTGAAGA
 W   I  A  E  P  T  K  E  P  I  V  D  E  D  D  D  V  A  E  E
      5780                5800                5820
AAGACAAAGAATTATTACTGGTGGAAATAAAACTGACATCTTAAGGCTACATGAACTAAC
 R  Q  R  I  I  T  G  G  N  K  T  D  I  L  R  L  H  E  L  T
      5840                5860                5880
CAAG|ATTTATCTGGGCACCTCCAGCCCAGCAGTGGACAGGCTGTGTGTCGGAGTTCGCCC
 K   I  Y  L  G  T  S  S  P  A  V  D  R  L  C  V  G  V  R  P
      5900                5920                5940
TGGAGAG|TGCTTTGGCCTCCTGGGAGTGAATGGTGCCGGCAAAACAACCACATTCAAGAT
 G  E   C  F  G  L  L  G  V  N  G  A  G  K  T  T  T  F  K  M
      5960                5980                6000
GCTCACTGGGGACACCACAGTGACCTCAGGGGATGCCACCGTAGCAGGCAAGAG|TATTTT
 L  T  G  D  T  T  V  T  S  G  D  A  T  V  A  G  K  S   I  L
      6020                6040                6060
AACCAATATTTCTGAAGTCCATCAAAATATGGGCTACTGTCCTCAGTTTGATGCAATCGA
 T  N  I  S  E  V  H  Q  N  M  G  Y  C  P  Q  F  D  A  I  D
      6080                6100                6120
TGAGCTGCTCACAGGACGAGAACATCTTTACCTTTATGCCCGGCTTCGAGGTGTACCAGC
 E  L  L  T  G  R  E  H  L  Y  L  Y  A  R  L  R  G  V  P  A
      6140                6160                6180
AGAAGAAATCGAAAAG|GTTGCAAACTGGAGTATTAAGAGCCTGGGCCTGACTGTCTACGC
 E  E  I  E  K   V  A  N  W  S  I  K  S  L  G  L  T  V  Y  A
      6200                6220                6240
CGACTGCCTGGCTGGCACGTACAGTGGGGGCAACAAGCGGAAACTCTCCACAGCCATCGC
 D  C  L  A  G  T  Y  S  G  G  N  K  R  K  L  S  T  A  I  A
      6260                6280                6300
ACTCATTGGCTGCCCACCGCTGGTGCTGCTG|GATGAGCCCACCACAGGGATGGACCCCCA
 L  I  G  C  P  P  L  V  L  L   D  E  P  T  T  G  M  D  P  Q
      6320                6240                6360
GGCACGCCGCATGCTGTGGAACGTCATCGTGAGCATCATCAGAAAAGGGAGGGCTGTGGT
 A  R  R  M  L  W  N  V  I  V  S  I  I  R  K  G  R  A  V  V
      6380                6400                6420
CCTCACATCCCACAG|CATGGAAGAATGTGAGGCACTGTGTACCCGGCTGGCCATCATGGT
 L  T  S  H  S   M  E  E  C  E  A  L  C  T  R  L  A  I  M  V
      6440                6460                6480
AAAGGGCGCCTTTCGATGTATGGGCACCATTCAGCATCTCAAGTCCAA|ATTTGGAGATGG
 K  G  A  F  R  C  M  G  T  I  Q  H  L  K  S  K   F  G  D  G
      6500                6520                6540
CTATATCGTCACAATGAAGATCAAATCCCCGAAGGACGACCTGCTTCCTGACCTGAACCC
 Y  I  V  T  M  K  I  K  S  P  K  D  D  L  L  P  D  L  N  P
```

FIG. 3G

```
      6560                6580                6600
TGTGGAGCAGTTCTTCCAGGGGAACTTCCCAGGCAGTGTGCAGAGGGAGAGGCACTACAA
 V  E  Q  F  F  Q  G  N  F  P  G  S  V  Q  R  E  R  H  Y  N
      6620                6640                6660
CATGCTCCAGTTCCAGGTCTCCTCCTCCTCCCTGGCGAGGATCTTCCAGCTCCTCCTCTC
 M  L  Q  F  Q  V  S  S  S  S  L  A  R  I  F  Q  L  L  L  S
      6680                6700                6720
CCACAAGGACAGCCTGCTCATCGAGGAGTACTCAGTCACACAGACCACACTGGACCAG|GT
 H  K  D  S  L  L  I  E  E  Y  S  V  T  Q  T  T  L  D  Q  V
      6740                6760                6780
GTTTGTAAATTTTGCTAAACAGCAGACTGAAAGTCATGACCTCCCTCTGCACCCTCGAGC
 F  V  N  F  A  K  Q  Q  T  E  S  H  D  L  P  L  H  P  R  A
      6800                6820                6840
TGCTGGAGCCAGTCGACAAGCCCAG|GACTGATCTTTCACACCGCTCGTTCCTGCAGCCAG
 A  G  A  S  R  Q  A  Q  D
      6860                6880                6900
AAAGGAACTCTGGGCAGCTGGAGGCGCAGGAGCCTGTGCCCATATGGTCATCCAAATGGA
      6920                6940                6960
CTGGCCCAGCGTAAATGACCCCACTGCAGCAGAAAACAAACACACGAGGAGCATGCAGCG
      6980                7000                7020
AATTCAGAAAGAGGTCTTTCAGAAGGAAACCGAAACTGACTTGCTCACCTGGAACACCTG
      7040                7060                7080
ATGGTGAAACCAAACAAATACAAAATCCTTCTCCAGACCCCAGAACTAGAAACCCCGGGC
      7100                7120                7140
CATCCCACTAGCAGCTTTGGCCTCCATATTGCTCTCATTTCAAGCAGATCTGCTTTTCTG
      7160                7180
CATGTTTGTCTGTGTGTCTGCGTTGTGTGTGATTTTCATGGAAA
```

FIG. 3H

```
Abc1 MACXPQLRLLLWKNLTFRRRQTCQLLLEVAWPLFIFLILSVRLSYPPYE 50
ABCR MGFVRQIQLLLWKNWTLRKRQKIRFVVELVWPLSLFLVLIWLRNANPLYS 50
Abc2 ..................................................  0
ABCC MAVLRQLALLLWKNYTLQKRKVLVTVLELFLPLLFSGILIWLRLKIQSEN 50

Abc1 QHECHFPNKAMPSAGTLPWVQGIICNANNPCFRYPTPGEAPGVVGNFNKS 100
ABCR HHECHFPNKAMPSAGMLPWLQGIFCNVNNPCFQSPTPGESPGIVSNYNNS 100
Abc2 ..................................................  0
ABCC VPNATIYPGQSIQELPLFFTFPPPGDTWELAYIPSHSDAAKTVTETVRRA 100

Abc1 IVSRLFSDAQRLLLYSQRDTSIKDMHKVLRMLRQIKH.........PNSN 141
ABCR ILARVYRDFQELLMNAPESQHLGRIWTELHILSQFMDTLRTHPERIAGRG 150
Abc2 ..................................................  0
ABCC LVINMRVRGFPSEKDFEDYIRYDNCSSSVLAAVVFEHPFNHSKEPLPLAV 150

Abc1 LKLQDFLVDNETFSGFLQHNLSLPRSTVDSLLQXNVGLQKVFLQGYQLHL 191
ABCR IRIRDILKDEETLTLFLIKNIGLSDSVVYLLINSQVRPEQFAHGVPDLAL 200
Abc2 ..................................................  0
ABCC KYHLRFSYTRRNYMWTQTGSFFLKETEGWH....................180

Abc1 ASL.CNGSKLEEIIQLGDAEVS.....ALCGLPRKKLDAAERVLRYNMDI 235
ABCR KDIACSEALLERFIIFSQRRGAKTVRYALCSLSQGTLQWIEDTLYANVDF 250
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 LK...PVVTKLNSTSHLPTQHLAEATTVLLDSLGGLAQELFSTKSWSDMR 282
ABCR FKLFRVLPTLLDSRSQGINLR...SWGGILSDMSPRIQEFIHRPSMQDLL 297
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 QEVMFLTNVNSSSSSTQIYQAVSRIVCGHPEGGGLKIKSLNWYEDNNYKA 332
ABCR WVTRPLMQNGGPETFTKLMGILSDLLCGYPEGGGSRVLSFNWYEDNNYKA 347
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 LFGGNNTEEDVDTFYDNSTTPYCNDLMKNLESSPLSRIIWKALKPLLVGK 382
ABCR FLGIDSTRKDPIYSYDRRTTSFCNALIQSLESNPLTKIAWRAAKPLLMGK 397
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 ILYTPDTPATRQVMAEVNKTFQELAVFHDLEGMWEELSPQIWTFMENSQE 432
ABCR ILYTPDSPAARRILKNANSTFEELEHVRKLVKAWEEVGPQIWYFFDNSTQ 447
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 MDLVRTLLDSRGNDQFWEQKLDGLDWTAQDIMAFLAKNPEDVQSPNGSVY 482
ABCR MNMIRDTLGNPTVKDFLNRQLGEEGITAEAILNFLYKGPRESQADDMANF 497
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 TWREAFNETNQAIQTISRFMECVNLNKLEPIPTEVRLINKSMELLDERKF 532
ABCR DWRDIFNITDRTLRLVNQYLECLVLDKFESYNDETQLTQRALSLLEENMF 547
Abc2 ..................................................  0
ABCC ..................................................180

Abc1 WAGIVFTGITPDSVELPHHVKYKIRMDIDNVERTNKIKDGYWDPGPRADP 582
ABCR WAGVVFPDMYPWTSSLPPHVKYKIRMDIDVVEKTNKIKDRYWDSGPRADP 597
Abc2 ..................................................  0
ABCC ..........................TTSLFPLFPNPGPREPT 197
```

FIG. 4A

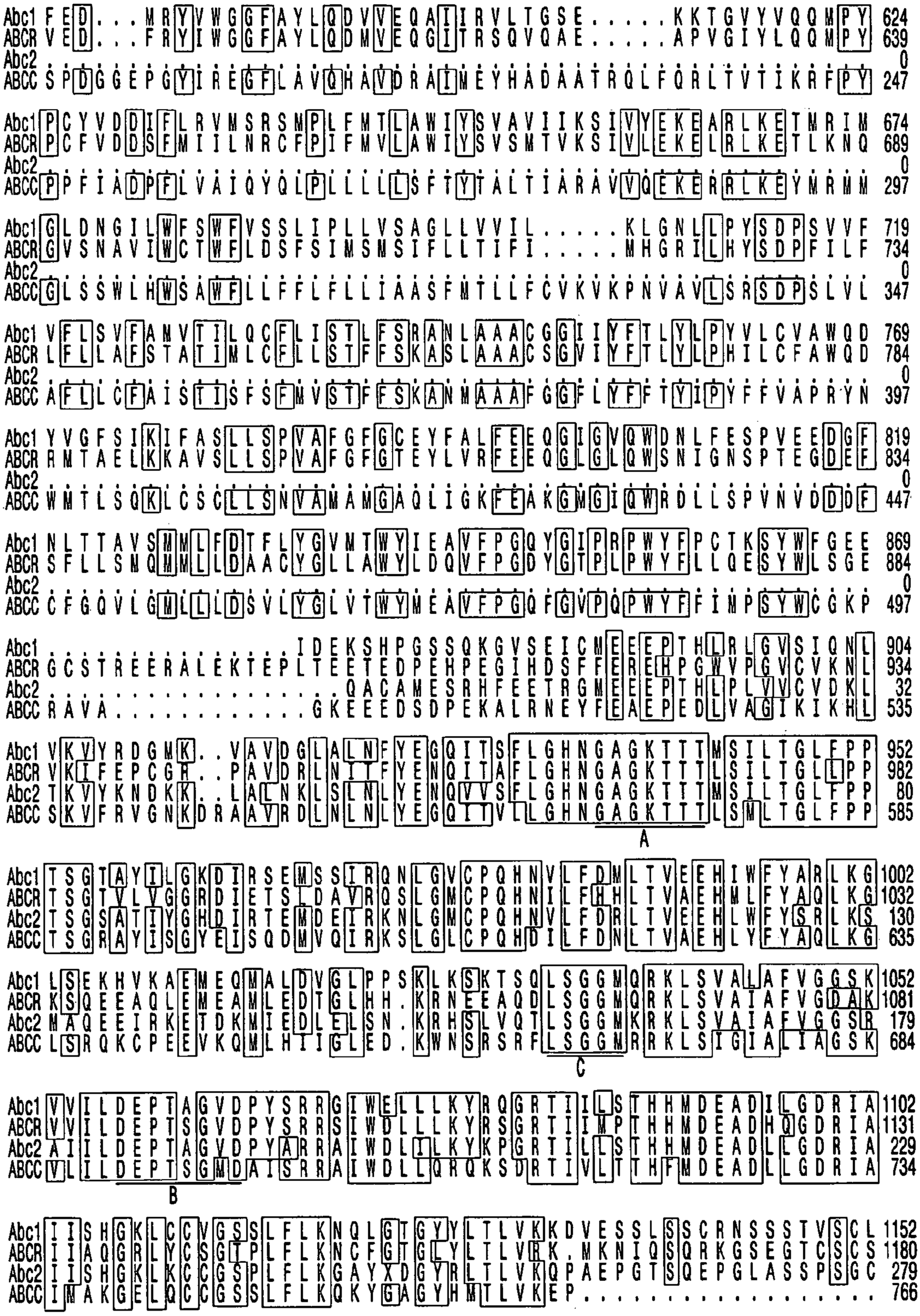


FIG. 4B

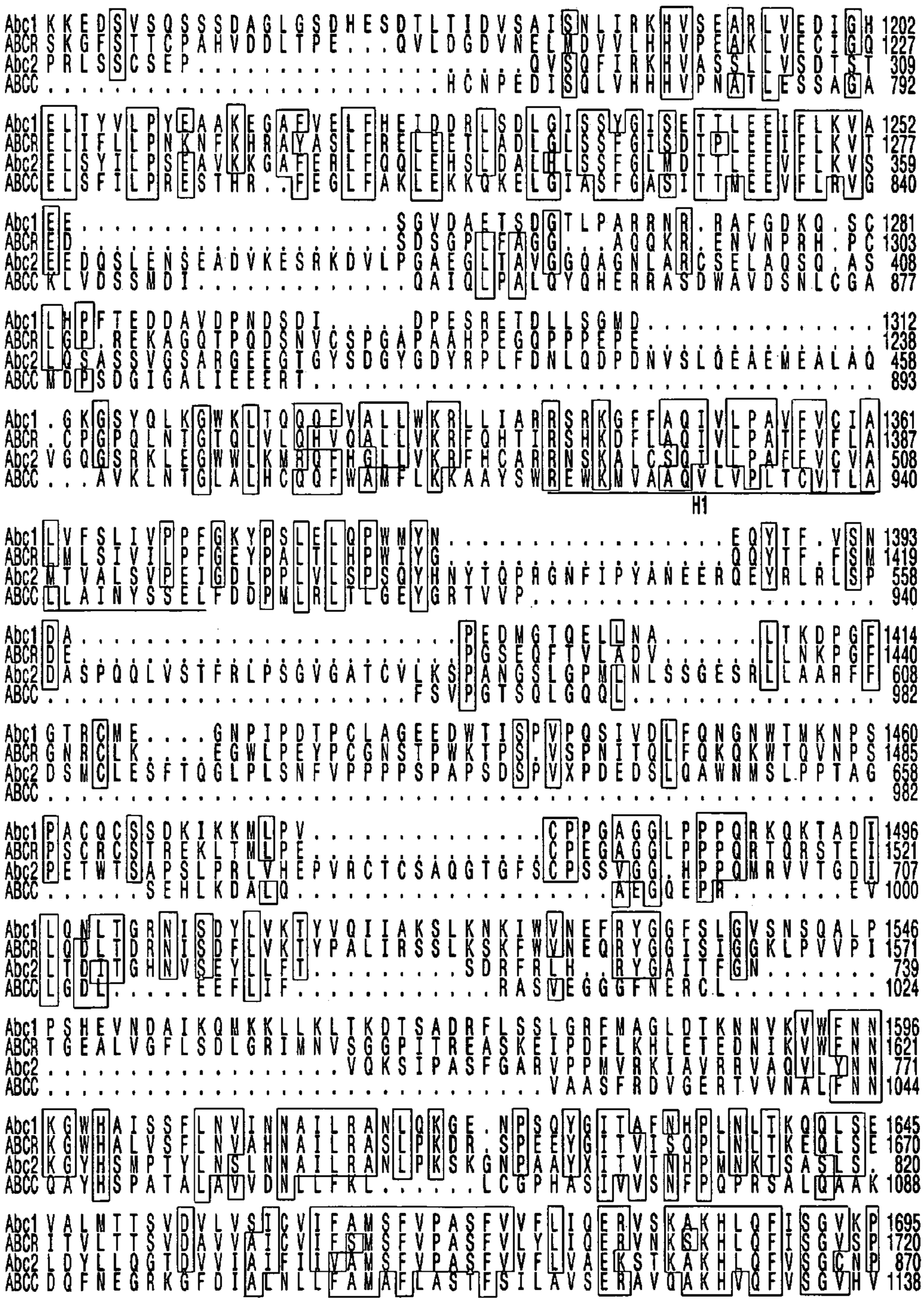


FIG. 4C

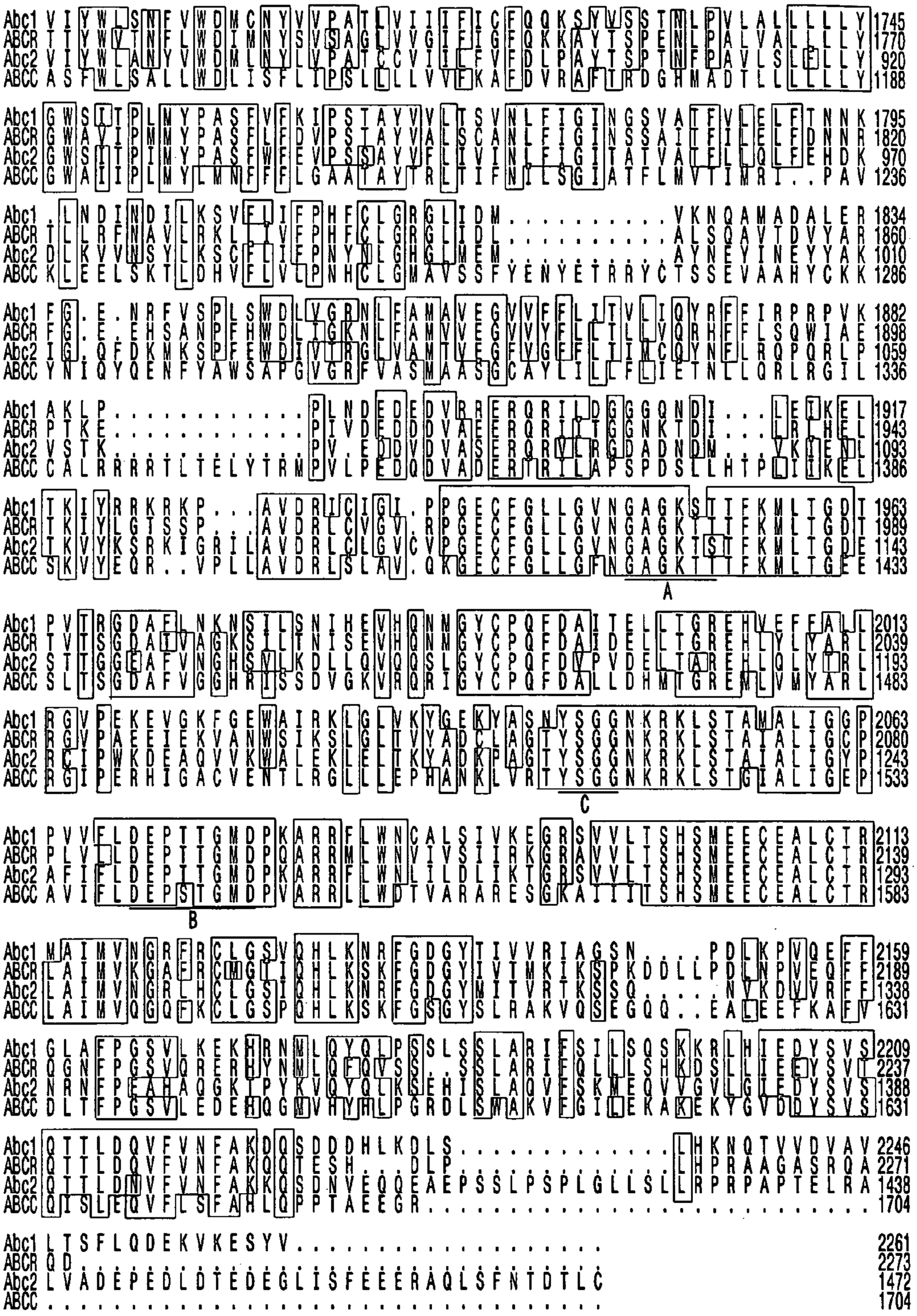


FIG. 4D

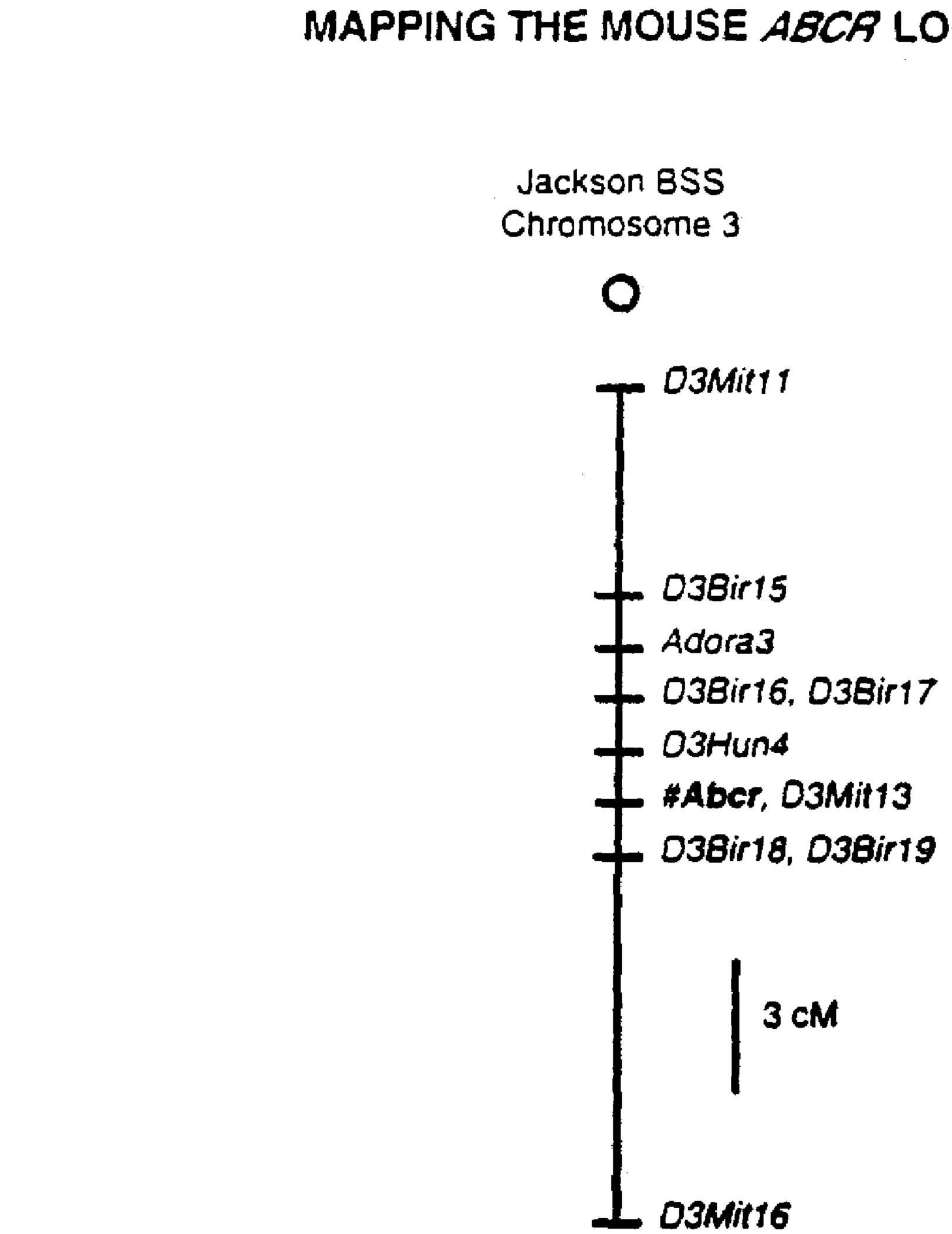

MAPPING THE MOUSE ABCR LOCUS
Jackson BSS
Chromosome 3
D3Mit11
D3Bir15
Adora3
D3Bir16, D3Bir17
D3Hun4
#Abcr, D3Mit13
D3Bir18, D3Bir19
3 cM
D3Mit16

FIG. 5

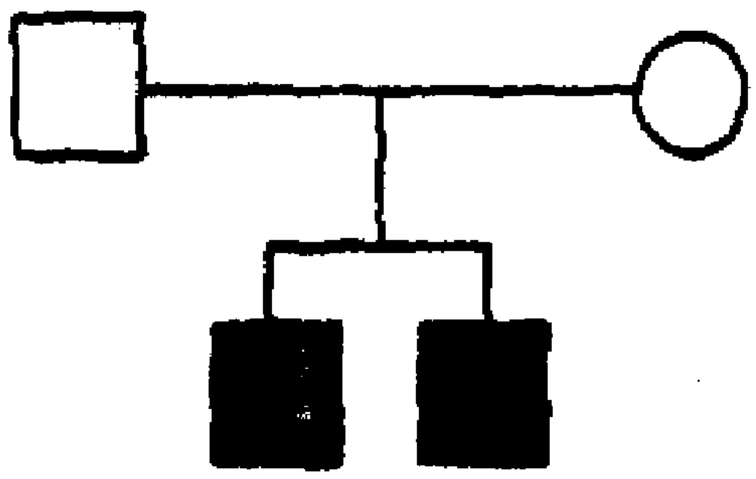


FIG. 6

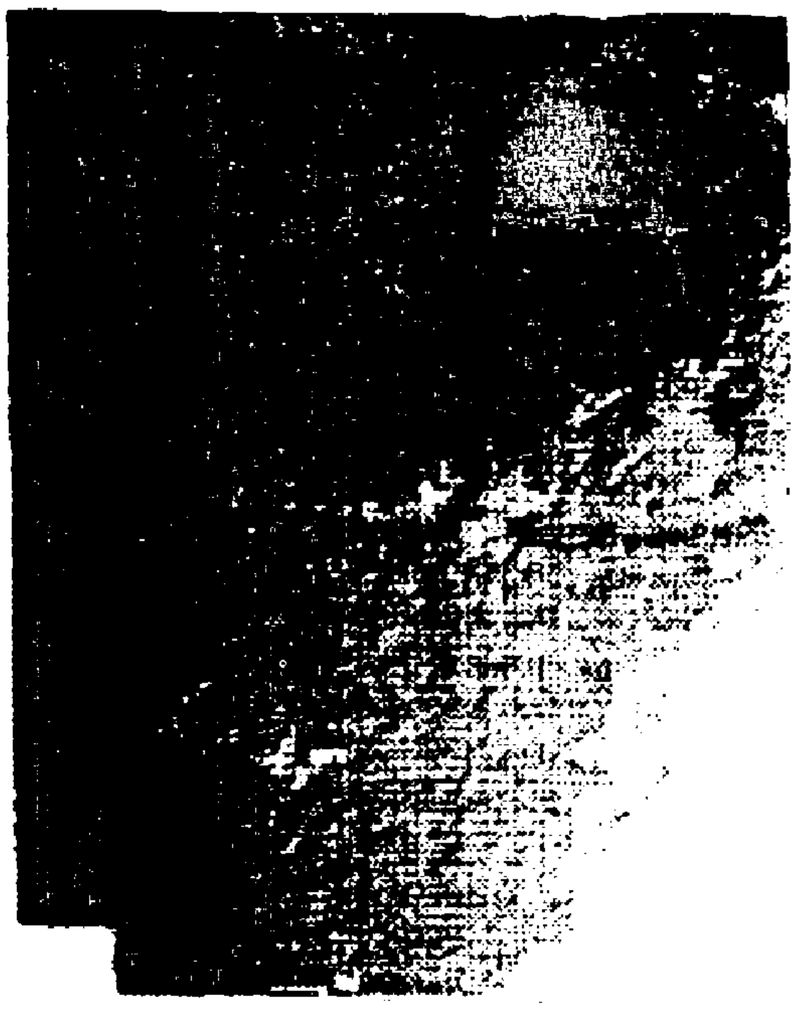


FIG. 7A

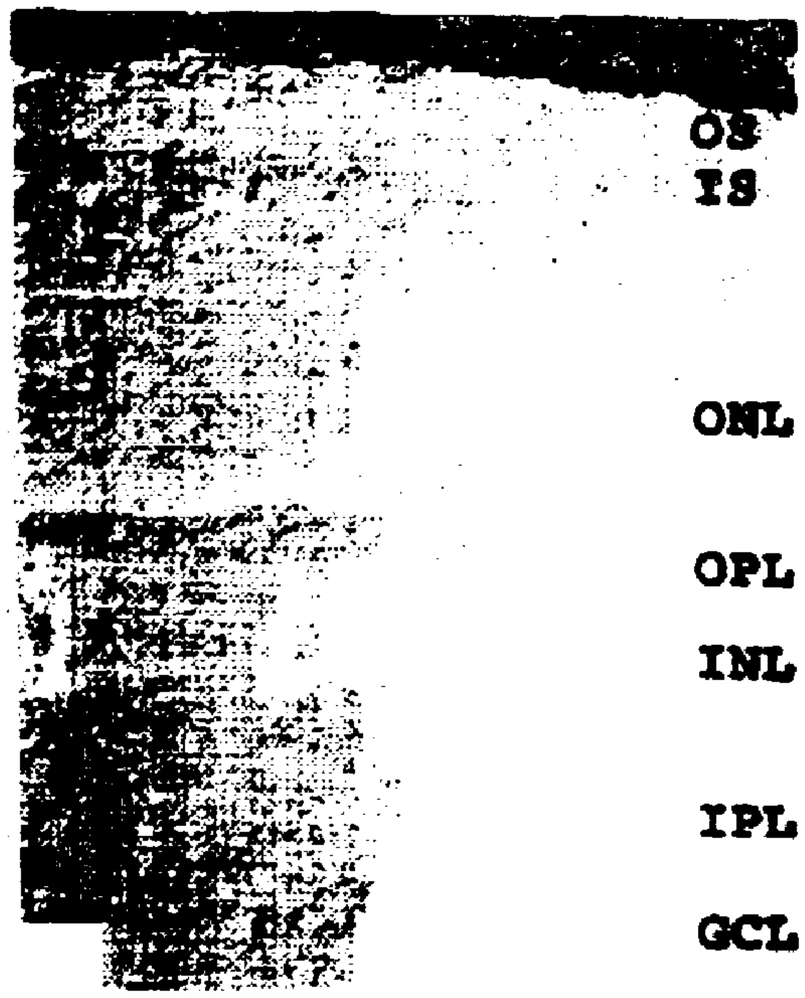


FIG. 7B

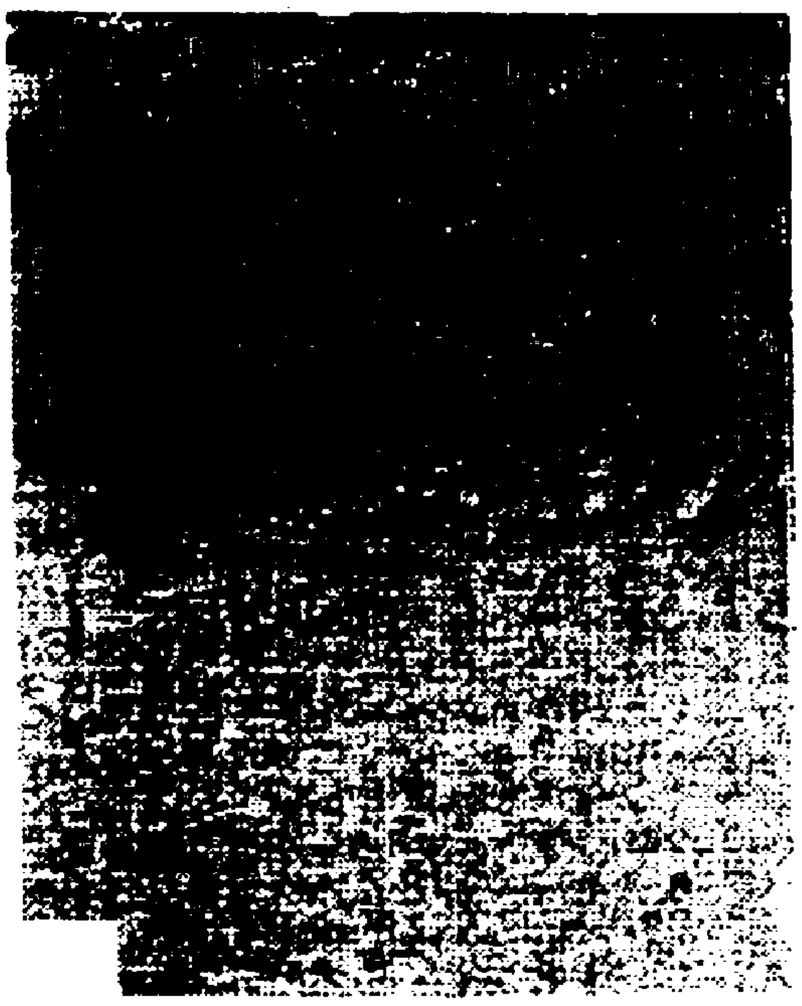


FIG. 7C

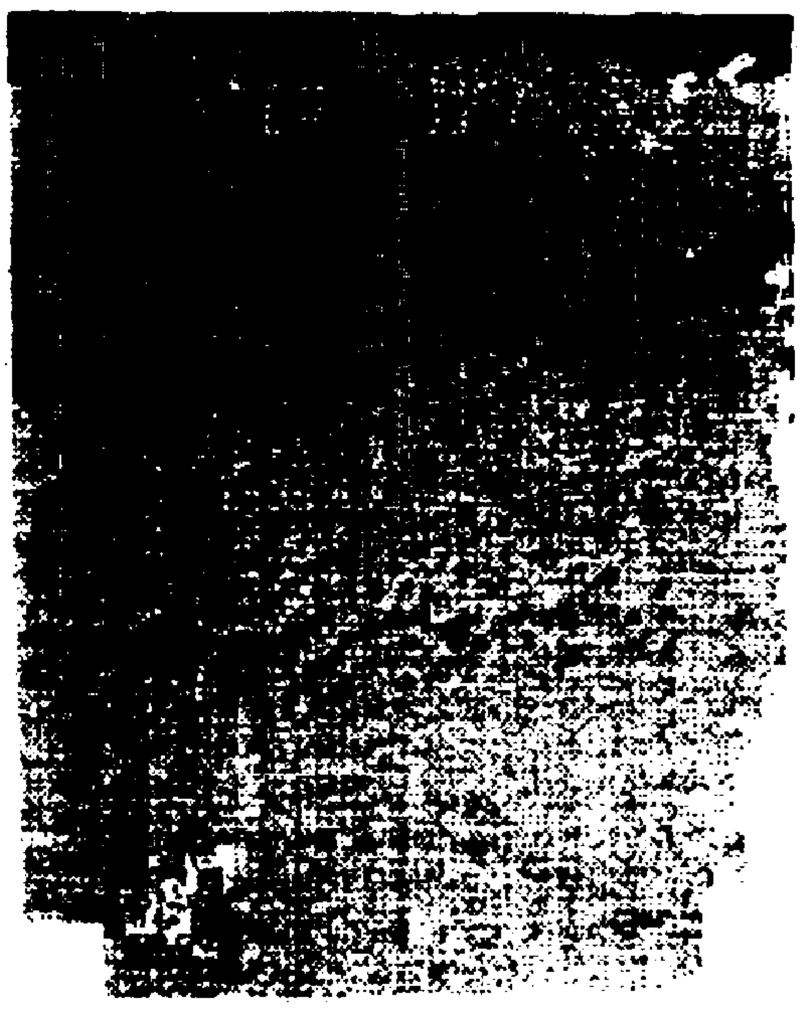


FIG. 7D

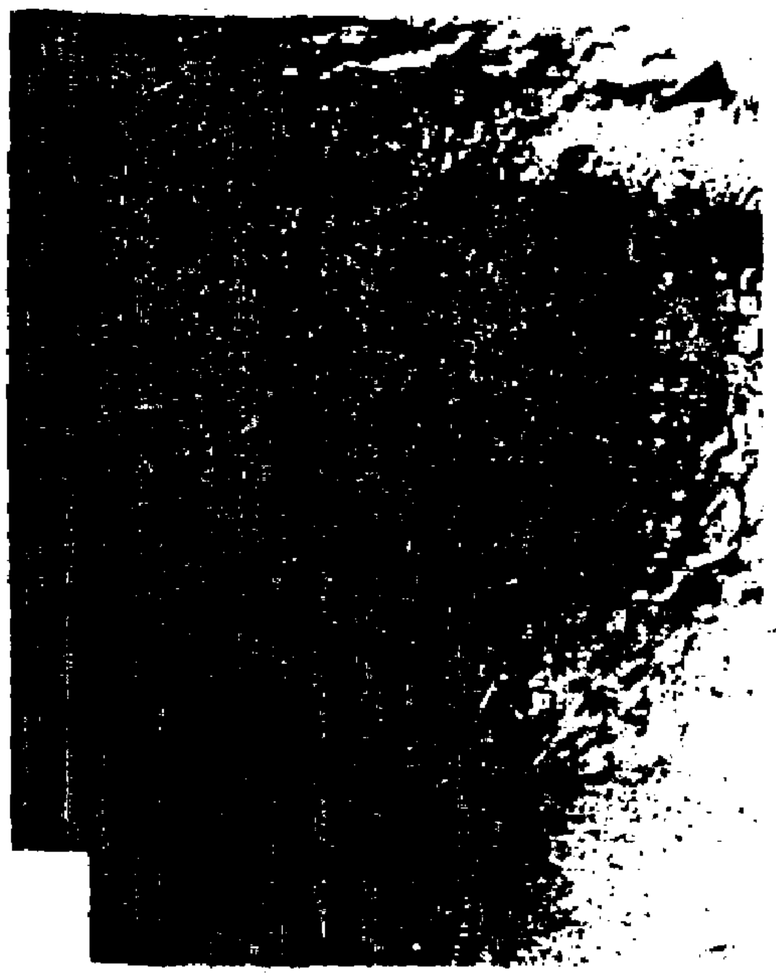


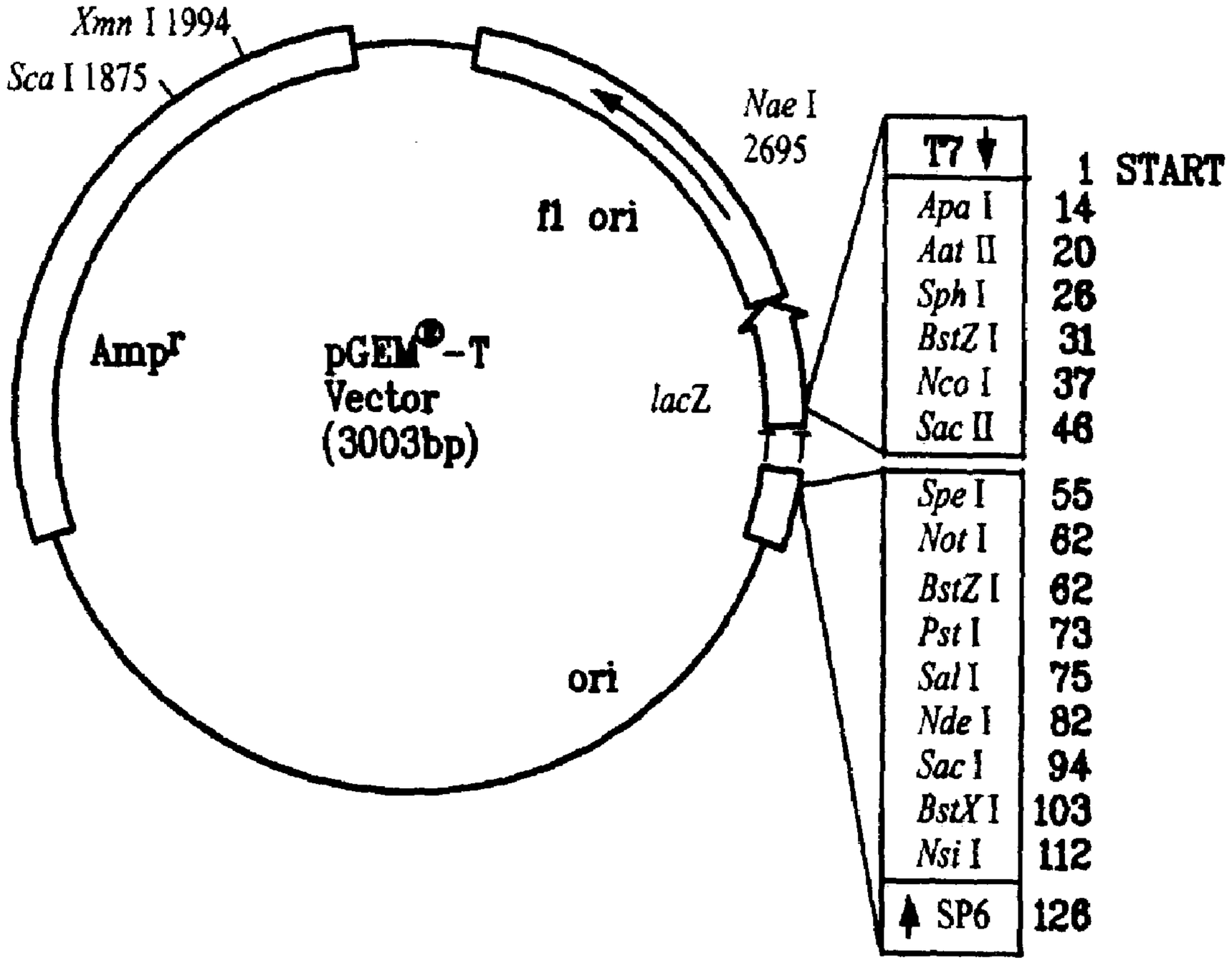
FIG. 7E

FIG. 7F

FIG. 7G

FIG. 7H

FIG. 8


Xmn I 1994
Sca I 1875
Nae I
2695
f1 ori
Amp^r
pGEM®-T
Vector
(3003bp)
lacZ
ori
T7
1 START
Apa I 14
Aat II 20
Sph I 26
BstZ I 31
Nco I 37
Sac II 46
Spe I 55
Not I 62
BstZ I 62
Pst I 73
Sal I 75
Nde I 82
Sac I 94
BstX I 103
Nsi I 112
SP6 126

NUCLEIC ACID AND AMINO ACID SEQUENCES FOR ATP-BINDING CASSETTE TRANSPORTER AND METHODS OF SCREENING FOR AGENTS THAT MODIFY ATP-BINDING CASSETTE TRANSPORTER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of and claims priority to U.S. non-provisional application Ser. No. 09/032,438, filed Feb. 27, 1998 now U.S. Pat. No. 6,713,300, and benefit of U.S. provisional application Ser. No. 60/039,388, filed Feb. 27, 1997. Each of these applications is hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This work was supported in part by research grants from the Department of Health and Human Services, grant numbers DHHS #2 T32GM07330-19 and #3 T32EY07102-0553, the National Institutes of Health, grant number M01-RR00064. The United States Government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

Macular degeneration affects approximately 1.7 million individuals in the U.S. and is the most common cause of acquired visual impairment in those over the age of 65. Stargardt disease (STGD; McKusick Mendelian Inheritance (MIM) #248200) is arguably the most common hereditary recessive macular dystrophy and is characterized by juvenile to young adult onset, central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, and the frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery (Stargardt, 1909; Anderson et al., 1995). A clinically similar retinal disorder (Fundus Flavimaculatus, FFM, Franceschetti, 1963) often displays later age of onset and slower progression (Fishman, 1976; Noble and Carr, 1979). From linkage analysis, it has been concluded that STGD and FFM are most likely allelic autosomal recessive disorders with slightly different clinical manifestations caused by mutation(s) of a gene at chromosome 1p13-p21 (Gerber et al., 1995; Anderson et al., 1995). The STGD gene has been localized to a 4 cM region flanked by the recombinant markers D1S435 and D1S236 and a complete yeast artificial chromosome (YAC) contig of the region has been constructed (Anderson et al., 1995). Recently, the location of the STGD/FFM locus on human chromosome 1p has been refined to a 2 cM interval between polymorphic markers D1S406 and D1S236 by genetic linkage analysis in an independent set of STGD families (Hoyng et al., 1996). Autosomal dominant disorders with somewhat similar clinical phenotypes to STGD, identified in single large North American pedigrees, have been mapped to chromosome 13q34 (STGD2; MIM #153900; Zhang et al., 1994) and to chromosome 6q11-q14 (STGD3; MIM #600110; Stone et al., 1994), although these conditions are not characterized by the pathognomonic dark choroid observed by fluorescein angiography (Gass, 1987).

Members of the superfamily of mammalian ATP binding cassette (ABC) transporters are being considered as possible candidates for human disease phenotypes. The ABC superfamily includes genes whose products are transmembrane proteins involved in energy-dependent transport of a wide spectrum of substrates across membranes (Childs and Ling, 1994; Dean and Allikmets, 1995). Many disease-causing members of this superfamily result in defects in the transport of specific substrates (CFTR, Riordan et al., 1989; ALD, Mosser et al., 1993; SUR, Thomas et al., 1995; PMP70, Shimozawa et al., 1992; TAP2, de la Salle et al., 1994). In eukaryotes, ABC genes encode typically four domains that include two conserved ATP-binding domains (ATP) and two domains with multiple transmembrane (TM) segments (Hyde et al. 1996). The ATP-binding domains of ABC genes contain motifs of characteristic conserved residues (Walker A and B motifs) spaced by 90–120 amino acids. Both this conserved spacing and the "Signature" or "C" motif just upstream of the Walker B site distinguish members of the ABC superfamily from other ATP-binding proteins (Hyde et al., 1990; Michaelis and Berkower, 1995). These features have allowed the isolation of new ABC genes by hybridization, degenerate PCR, and inspection of DNA sequence databases (Allikmets et al., 1993, 1995; Dean et al., 1994; Luciani et al., 1994).

The characterization of twenty-one new members of the ABC superfamily may permit characterization and functions assigned to these genes by determining their map locations and their patterns of expression (Allikmets et al., 1996). That many known ABC genes are involved in inherited human diseases suggests that some of these new loci will also encode proteins mutated in specific genetic disorders. Despite regionally localizing a gene by mapping, the determination of the precise localization and sequence of one gene nonetheless requires choosing the certain gene from about 250 genes, four to about five million base pairs, from within the regionally localized chromosomal site.

While advancements have been made as described above, mutations in retina-specific ABC transporter (ABCR) in patients with recessive macular dystrophy STGD/FFM have not yet been identified to Applicant's knowledge. That ABCR expression is limited to photoreceptors, as determined by the present invention, provides evidence as to why ABCR has not yet been sequenced. Further, the ABC1 subfamily of ABC transporters is not represented by any homolog in yeast (Michaelis and Berkower, 1995), suggesting that these genes evolved to perform specialized functions in multicellular organisms, which also lends support to why the ABCR gene has been difficult to identify. Unlike ABC genes in bacteria, the homologous genes in higher eukaryotes are much less well studied. The fact that prokaryotes contain a large number of ABC genes suggests that many mammalian members of the superfamily remain uncharacterized. The task of studying eukaryote ABC genes is more difficult because of the significantly higher complexity of eukaryotic systems and the apparent difference in function of even highly homologous genes. While ABC proteins are the principal transporters of a number of diverse compounds in bacterial cells, in contrast, eukaryotes have evolved other mechanisms for the transport of many amino acids and sugars. Eukaryotes have other reasons to diversify the role of ABC genes, for example, performing such functions as ion transport, toxin elimination, and secretion of signaling molecules.

Accordingly, there remains a need for the identification of the sequence of the gene, which in mutated forms is associated with retinal and/or macular degenerative diseases, including Stargardt Disease and Fundus Flavimaculatus, for example, in order to provide enhanced diagnoses and improved prognoses and interventional therapies for individuals affected with such diseases.

SUMMARY OF THE INVENTION

The present invention provides sequences encoding an ATP binding cassette transporter. Nucleic acid sequences, including SEQ ID NO: 1 which is a genomic sequence, and SEQ ID NOS: 2 and 5 which are cDNA sequences, are sequences to which the present invention is directed.

A further aspect of the present invention provides ATP binding cassette transporter polypeptides and/or proteins. SEQ ID NOS: 3 and 6 are novel polypeptides of the invention produced from nucleotide sequences encoding the ATP binding cassette transporter. Also within the scope of the present invention is a purified ATP binding cassette transporter.

The present invention also provides an expression vector comprising a nucleic acid sequence encoding an ATP binding cassette transporter, a transformed host cell capable of expressing a nucleic acid sequence encoding an ATP binding cassette transporter, a cell culture capable of expressing an ATP binding cassette transporter, and a protein preparation comprising an ATP binding cassette transporter.

The present invention is also directed to a method of screening for an agent that modifies ATP binding cassette transporter comprising combining purified ATP binding cassette transporter with an agent suspected of modifying ATP binding cassette transporter and observing a change in at least one characteristic associated with ATP binding cassette transporter. The present invention provides methods of identifying an agent that inhibits macular degeneration comprising combining purified ATP binding cassette transporter from a patient suspected of having macular degeneration and an agent suspected interacting with the ATP binding cassette transporter and observing an inhibition in at least one of the characteristics of diseases associated with the ATP binding cassette transporter. In addition, the present invention provides for methods of identifying an agent that induces onset of at least one characteristic associated with ATP binding cassette transporter comprising combining purified wild-type ATP binding cassette transporter with an agent suspected of inducing a macular degenerative disease and observing the onset of a characteristic associated with macular degeneration.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. **1**A and **1**B displays the ABCR gene and amplification products. FIG. **1**A displays a physical map of the ABCR gene. Mega-YAC clones from the CEPH mega-YAC genomic library (Bellane-Chantelot et al., 1992) encompassing the 4cM critical region for STGD are represented by horizontal bars with shaded circles indicating confirmed positives for STSs by landmark mapping. The individual STS markers and their physical order are shown below the YACs with arrows indicating the centromeric (cen) and telomeric (1pter) direction (Anderson et al., 1995). The horizontal double head arrow labeled STGD indicates the refined genetic interval delineated by historical recombinants (Anderson et al., 1995). FIG. **1**B displays the results of agarose gel electrophoresis of PCR amplification products with primers from the 5' (GGTCTTCGTGTGTGGTCATT, SEQ ID NO: 114, GGTCCAGTTCTTCCAGAG, SEQ ID NO: 115, labeled 5' ABCR) or 3' (ATCCTCTGACTCAGCAATCACA, SEQ ID NO: 116, TTGCAATTACAAATGCAATGG, SEQ ID NO: 117, labeled 3' ABCR) regions of ABCR on the 13 different YAC DNA templates indicated as diagonals above the gel. The asterisk denotes that YAC 680_b__5 was positive for the 5' ABCR PCR but negative for the 3' ABCR PCR. These data suggest the ABCR gene maps within the interval delineated by markers D1S3361–D1S236 and is transcribed toward the telomere, as depicted by the open horizontal box.

FIG. **2** exhibits the size and tissue distribution of ABCR transcripts in the adult rat. A blot of total RNA from the indicated tissues was hybridized with a 1.6 kb mouse Abcr probe (top) and a ribosomal protein S26 probe (bottom; Kuwano et al., 1985). The ABCR probe revealed a predominant transcript of approximately 8 kb that is found in retina only. The mobility of the 28S and 18S ribosomal RNAs are indicated at the right. B, brain; H, heart; K, kidney; Li, liver; Lu, lung; R, retina; S, spleen.

FIGS. **3**A–H shows the sequence of the ABCR coding region within the genomic ABCR sequence, SEQ ID NO: 1. The sequence of the ABCR cDNA, SEQ ID NO: 2, is shown with the predicted protein sequence, SEQ ID NO: 3, in one-letter amino acid code below. The location of splice sites is shown by the symbol |.

FIGS. **4**A–D displays the alignment of the ABCR protein, SEQ ID NO:3, with other members of the ABC1 subfamily. The deduced amino acid sequence of ABCR is shown aligned to known human and mouse proteins that are members of the same subfamily. Abc1, mouse Abc1 (SEQ ID NO:118); Abc2, mouse Abc2 (SEQ ID NO:119); and ABCC, human ABC gene (SEQ ID NO:120). The Walker A and B motifs and the Signature motif C are designated by underlining and the letters A, B, and C, respectively.

FIG. **5** exhibits the location of Abcr from a Jackson BSS Backcross showing a portion of mouse chromosome 3. The map is depicted with the centromere toward the top. A 3 cM scale bar is also shown. Loci mapping to the same position are listed in alphabetical order.

FIG. **6** shows the segregation of SSCP variants in exon 49 of the ABCR gene in kindred AR293. Sequence analysis of SSCP bands revealed the existence of wild-type sequence (bands 1 and 3) and mutant sequence (bands 2 and 4). DNA sequencing revealed a 15 base pair deletion, while the affected children (lanes 2 and 3) are homozygous. Haplotype analysis demonstrated homozygosity at the STGD locus in the two affected individuals.

FIGS. **7**A–H shows the localization of ABCR transcripts to photoreceptor cells. In situ hybridization was performed with digoxygenin-labeled riboprobes and visualized using an alkaline phosphatase conjugated anti-digoxygenin antibody. FIGS. **7**A–D displays hybridization results of retina and choroid from a pigmented mouse (C57/B16); FIGS. **7**E and **7**F shows hybridization results of retina and choroid from an albino rat; and FIGS. **7**G and **7**H exhibits hybridization results of retina from a macaque monkey. FIGS. **7**A, **7**E, and **7**G display results from a mouse abcr antisense probe; FIG. **7**B exhibit results from a mouse abcr sense probe; FIG. **7**C shows results from a macaque rhodopsin antisense probe; and FIGS. **7**D, **7**F, and **7**H display results from a mouse blue cone pigment antisense probe. ABCR transcripts are localized to the inner segments of the photoreceptor cell layer, a pattern that matches the distribution of rhodopsin transcripts but is distinct from the distribution of cone visual pigment transcripts. Hybridization is not observed in the RPE or choroid, as seen most clearly in the albino rat eye (arrowhead in FIG. **7**E). The retinal layers indicated in FIG. **7**B are: OS, outer segments; IS, inner segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer.

FIG. **8** provides a pGEM®-T Vector map.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to the nucleic acid and protein sequences encoding ATP binding cassette transporter. The ATP binding cassette transporter of the present invention is retina specific ATP binding cassette transporter (ABCR); more particularly, ABCR may be isolated from retinal cells, preferably photoreceptor cells. The present invention provides nucleotide sequences of ABCR including genomic sequences, SEQ ID NO: 1, and cDNA sequences SEQ ID NO: 2 and 5. Novel polypeptide sequences, SEQ ID NOS: 3 and 6, for ABCR, are the translated products of SEQ ID NOS: 2 and 5, respectively, and are also included in the present invention.

SEQ ID NO:1 provides the human genomic DNA sequence of ABCR. SEQ ID NOS: 2 and 5 provide wild-type cDNA sequences of human ABCR, which result in translated products SEQ ID NOS: 3 and 6, respectively. While not intending to be bound by any particular theory or theories of operation, it is believed that SEQ ID NOS: 2 and 5 are isoforms of ABCR cDNA. The difference between SEQ ID NOS: 2 and 5 may be accounted for by an additional sequence in SEQ ID NO: 2 which is added between bases 4352 and 4353 of SEQ ID NO: 5. This difference is thought to arise from alternative splicing of the nascent transcript of ABCR, in which an alternative exon 30, SEQ ID NO: 4, is excluded. This alternative exon encodes an additional 38 amino acids, SEQ ID NO: 11.

Nucleic acids within in the scope of the present invention include cDNA, RNA, genomic DNA, fragments or portions within the sequences, antisense oligonucleotides. Sequences encoding the ABCR also include amino acid, polypeptide, and protein sequences. Variations in the nucleic acid and polypeptide sequences of the present invention are within the scope of the present invention and include N terminal and C terminal extensions, transcription and translation modifications, and modifications in the cDNA sequence to facilitate and improve transcription and translation efficiency. In addition, changes within the wild-type sequences identified herein which changed sequence retains substantially the same wild-type activity, such that the changed sequences are substantially similar to the ABCR sequences identified, are also considered within the scope of the present invention. Mismatches, insertions, and deletions which permit substantial similarity to the ABCR sequences, such as similarity in residues in hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. In addition, the isolated, or purified, sequences of the present invention may be natural, recombinant, synthetic, or a combination thereof. Wild-type activity associated with the ABCR sequences of the present invention include, inter alia, all or part of a sequence, or a sequence substantially similar thereto, that codes for ATP binding cassette transporter.

The genomic, SEQ ID NO: 1, and cDNA, SEQ ID NOS: 2 and 5, sequences are identified in FIG. **3** and encode ABCR, certain mutations of which are responsible for the class of retinal disorders known as retinal or macular degenerations. Macular degeneration is characterized by macular dystrophy, various alterations of the peripheral retina, central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery, and subretinal deposition of lipofuscin-like material. Retinal and macular degenerative diseases include and are not limited to Stargardt Disease, Fundus Flavimaculatus, age-related macular degeneration, and may include disorders variously called retinitis pigmentosa, combined rod and cone dystrophies, cone dystrophies and degenerations, pattern dystrophy, bull's eye maculopathies, and various other retinal degenerative disorders, some induced by drugs, toxins, environmental influences, and the like. Stargardt Disease is an autosomal recessive retinal disorder characterized by juvenile to adult-onset macular and retinal dystrophy. Fundus Flavimaculatus often displays later age of onset and slower progression. Some environmental insults and drug toxicities may create similar retinal degenerations. Linkage analysis reveals that Stargardt Disease and Fundus Flavimaculatus may be allelic autosomal recessive disorders with slightly different clinical manifestations. The identification of the ABCR gene suggests that different mutations within ABCR may be responsible for these clinical phenomena.

The present invention is also directed to a method of screening for an agent that modifies ATP binding cassette transporter comprising combining purified ATP binding cassette transporter with an agent suspected of modifying ATP binding cassette transporter and observing a change in at least one characteristic associated with ATP binding cassette transporter.

"Modify" and variations thereof include changes such as and not limited to inhibit, suppress, delay, retard, slow, suspend, obstruct, and restrict, as well as induce, encourage, provoke, and cause. Modify may also be defined as complete inhibition such that macular degeneration is arrested, stopped, or blocked. Modifications may, directly or indirectly, inhibit or substantially inhibit, macular degeneration or induce, or substantially induce, macular degeneration, under certain circumstances.

Methods of identifying an agent that inhibits macular degeneration are embodied by the present invention and comprise combining purified ATP binding cassette transporter from a patient suspected of having macular degeneration and an agent suspected of interacting with the ATP binding cassette transporter and observing an inhibition in at least one of the characteristics of diseases associated with the ATP binding cassette transporter. Accordingly, such methods serve to reduce or prevent macular degeneration, such as in human patients. In addition, the present invention provides for methods of identifying an agent that induces onset of at least one characteristic associated with ATP binding cassette transporter comprising combining purified wild-type ATP binding cassette transporter with an agent suspected of inducing a macular degenerative disease and observing the onset of a characteristic associated with macular degeneration. Thus, such methods provide methods of using laboratory animals to determine causative agents of macular degeneration. The ATP binding cassette transporter may be provided for in the methods identified herein in the form of nucleic acids, such as and not limited to SEQ ID NOS: 1, 2, and 5 or as an amino acid, SEQ ID NOS: 3 and 6, for example. Accordingly, transcription and translation inhibitors may be separately identified. Characteristics associated with macular degeneration include and are not limited to central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, and the frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery. Accordingly, observing one or more of the characteristics set forth above results in identification of an agent that induces macular degeneration, whereas reduction or inhibition of at least one of the characteristics results in identification of an agent that inhibits macular degeneration.

Mutational analysis of ABCR in Stargardt Disease families revealed thus far seventy four mutations including fifty four single amino acid substitutions, five nonsense mutations resulting in early truncation of the protein, six frame shift mutations resulting in early truncation of the protein, three in-frame deletions resulting in loss of amino acid residues from the protein, and six splice site mutations resulting in incorrect processing of the nascent RNA transcript, see Table 2. Compound heterozygotes for mutations in ABCR were found in forty two families. Homozygous mutations were identified in three families with consanguineous parentage. Accordingly, mutations in wild-type ABCR which result in activities that are not associated with wild-type ABCR are herein referred to as sequences which are associated with macular degeneration. Such mutations include missense mutations, deletions, insertions, substantial differences in hydrophobicity, hydrophilicity, acidity, and basicity. Characteristics which are associated with retinal or macular degeneration include and are not limited to those characteristics set forth above.

Mutations in wild-type ABCR provide a method of detecting macular degeneration. Retinal or macular degeneration may be detected by obtaining a sample comprising patient nucleic acids from a patient tissue sample; amplifying retina-specific ATP binding cassette receptor specific nucleic acids from the patient nucleic acids to produce a test fragment; obtaining a sample comprising control nucleic acids from a control tissue sample; amplifying control nucleic acids encoding wild-type retina-specific ATP binding cassette receptor to produce a control fragment; comparing the test fragment with the control fragment to detect the presence of a sequence difference in the test fragment, wherein a difference in the test fragment indicates macular degeneration. Mutations in the test fragment, including and not limited to each of the mutations identified above, may provide evidence of macular degeneration.

A purified ABCR protein is also provided by the present invention. The purified ABCR protein may have an amino acid sequence as provided by SEQ ID NOS: 3 and 6.

The present invention is directed to ABCR sequences obtained from mammals from the Order Rodentia, including and not limited to hamsters, rats, and mice; Order Logomorpha, such as rabbits; more particularly the Order Carnivora, including Felines (cats) and Canines (dogs); even more particularly the Order Artiodactyla, Bovines (cows) and Suines (pigs); and the Order Perissodactyla, including Equines (horses); and most particularly the Order Primates, Ceboids and Simoids (monkeys) and Anthropoids (humans and apes). The mammals of most preferred embodiments are humans.

Generally, the sequences of the invention may be produced in host cells transformed with an expression vector comprising a nucleic acid sequence encoding ABCR. The transformed cells are cultured under conditions whereby the nucleic acid sequence coding for ABCR is expressed. After a suitable amount of time for the protein to accumulate, the protein may be purified from the transformed cells.

A gene coding for ABCR may be obtained from a cDNA library. Suitable libraries can be obtained from commercial sources such as Clontech, Palo Alto, Calif. Libraries may also be prepared using the following non-limiting examples: hamster insulin-secreting tumor (HIT), mouse αTC-6, and rat insulinoma (RIN) cells. Positive clones are then subjected to DNA sequencing to determine the presence of a DNA sequence coding for ABCR. DNA sequencing is accomplished using the chain termination method of Sanger et al., *Proc. Nat'l. Acad. Sci, U.S.A.*, 1977, 74, 5463. The DNA sequence encoding ABCR is then inserted into an expression vector for later expression in a host cell.

Expression vectors and host cells are selected to form an expression system capable of synthesizing ABCR. Vectors including and not limited to baculovirus vectors may be used in the present invention. Host cells suitable for use in the invention include prokaryotic and eukaryotic cells that can be transformed to stably contain and express ABCR. For example, nucleic acids coding for the recombinant protein may be expressed in prokaryotic or eukaryotic host cells, including the most commonly used bacterial host cell for the production of recombinant proteins, *E. coli*. Other microbial strains may also be used, however, such as *Bacillus subtilis*, and other enterobacteriaceae such as *Salmonella typhimurium* or *Serratia marcescens*, various species of *Pseudomonas,* or other bacterial strains.

The preferable eukaryotic system is yeast, such as *Saccharomyces cerevisiae*. Yeast artificial chromosome (YAC) systems are able to accommodate the large size of ABCR gene sequence or genomic clone. The principle of the YAC system is similar to that used in conventional cloning of DNA. Large fragments of cDNA are ligated into two "arms" of a YAC vector, and the ligation mixture is then introduced into the yeast by transformation. Each of the arms of the YAC vector carries a selectable marker as well as appropriately oriented sequences that function as telomeres in yeast. In addition, one of the two arms carries two small fragments that function as a centromere and as an origin of replication (also called an ARS element-autonomously replicating sequences). Yeast transformants that have taken up and stably maintained an artificial chromosome are identified as colonies on agar plates containing the components necessary for selection of one or both YAC arms. YAC vectors are designed to allow rapid identification of transformants that carry inserts of genomic DNA. Insertion of genomic DNA into the cloning site interrupts a suppressor tRNA gene and results in the formation of red rather than white colonies by yeast strains that carry an amber ade2 gene.

To clone in YAC vectors, genomic DNA from the test organism is prepared under conditions that result in relatively little shearing such that its average size is several million base pairs. The cDNA is then ligated to the arms of the YAC vector, which has been appropriately prepared to prevent self-ligation. As an alternative to partial digestion with EcoRI, YAC vectors may be used that will accept genomic DNA that has been digested to completion with rarely cutting restriction enzymes such as NotI or MluI.

In addition, insect cells, such as *Spodoptera frugiperda;* chicken cells, such as E3C/O and SL-29; mammalian cells, such as HeLa, Chinese hamster ovary cells (CHO), COS-7 or MDCK cells and the like may also be used. The foregoing list is illustrative only and is not intended in any way to limit the types of host cells suitable for expression of the nucleic acid sequences of the invention.

As used herein, expression vectors refer to any type of vector that can be manipulated to contain a nucleic acid sequence coding for ABCR, such as plasmid expression vectors, viral vectors, and yeast expression vectors. The selection of the expression vector is based on compatibility with the desired host cell such that expression of the nucleic acid encoding ABCR results. Plasmid expression vectors comprise a nucleic acid sequence of the invention operably linked with at least one expression control element such as a promoter. In general, plasmid vectors contain replicon and control sequences derived from species compatible with the host cell. To facilitate selection of plasmids containing nucleic acid sequences of the invention, plasmid vectors

may also contain a selectable marker such as a gene coding for antibiotic resistance. Suitable examples include the genes coding for ampicillin, tetracycline, chloramphenicol, or kanamycin resistance.

Suitable expression vectors, promoters, enhancers, and other expression control elements are known in the art and may be found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, second edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), incorporated herein by reference in its entirety.

Transformed host cells containing a DNA sequence encoding ABCR may then be grown in an appropriate medium for the host. The cells are then grown until product accumulation reaches desired levels at which time the cells are then harvested and the protein product purified in accordance with conventional techniques. Suitable purification methods include, but are not limited to, SDS PAGE electrophoresis, phenylboronate-agarose, reactive green 19-agarose, concanavalin A sepharose, ion exchange chromatography, affinity chromatography, electrophoresis, dialysis and other methods of purification known in the art.

Protein preparations, of purified or unpurified ABCR by host cells, are accordingly produced which comprise ABCR and other material such as host cell components and/or cell medium, depending on the degree of purification of the protein.

The invention also includes a transgenic non-human animal, including and not limited to mammals, such as and not limited to a mouse, rat, or hamster, comprising a sequence encoding ABCR, or fragment thereof that substantially retains ABCR activity, introduced into the animal or an ancestor of the animal. The sequence may be wild-type or mutant and may be introduced into the animal at the embryonic or adult stage. The sequence is incorporated into the genome of an animal such that it is chromosomally incorporated into an activated state. A transgenic non-human animal has germ cells and somatic cells that contain an ABCR sequence. Embryo cells may be transfected with the gene as it occurs naturally, and transgenic animals are selected in which the gene has integrated into the chromosome at a locus which results in activation. Other activation methods include modifying the gene or its control sequences prior to introduction into the embryo. The embryo may be transfected using a vector containing the gene.

In addition, a transgenic non-human animal may be engineered wherein ABCR is suppressed. For purposes of the present invention, suppression of ABCR includes, and is not limited to strategies which cause ABCR not to be expressed. Such strategies may include and are not limited to inhibition of protein synthesis, pre-mRNA processing, or DNA replication. Each of the above strategies may be accomplished by antisense inhibition of ABCR gene expression. Many techniques for transferring antisense sequences into cells are known to those of skill, including and not limited to microinjection, viral-mediated transfer, somatic cell transformation, transgene integration, and the like, as set forth in Pinkert, Carl, *Transgenic Animal Technology*, 1994, Academic Press, Inc., San Diego, Calif., incorporated herein by reference in its entirety.

Further, a transgenic non-human animal may be prepared such that ABCR is knocked out. For purposes of the present invention, a knock-out includes and is not limited to disruption or rendering null the ABCR gene. A knock-out may be accomplished, for example, with antisense sequences for ABCR. The ABCR gene may be knocked out by injection of an antisense sequence for all or part of the ABCR sequence such as an antisense sequence for all or part of SEQ ID NO: 2. Once ABCR has been rendered null, correlation of the ABCR to macular degeneration may be tested. Sequences encoding mutations affecting the ABCR may be inserted to test for alterations in various retinal and macular degenerations exhibited by changes in the characteristics associated with retinal and macular degeneration. ANABCR knock-out may be engineered by inserting synthetic DNA into the animal chromosome by homologous recombination. In this method, sequences flanking the target and insert DNA are identical, allowing strand exchange and crossing over to occur between the target and insert DNA. Sequences to be inserted typically include a gene for a selectable marker, such as drug resistance. Sequences to be targeted are typically coding regions of the genome, in this case part of the ABCR gene. In this process of homologous recombination, targeted sequences are replaced with insert sequences thus disrupting the targeted gene and rendering it nonfunctional. This nonfunctional gene is called a null allele of the gene.

To create the knockout mouse, a DNA construct containing the insert DNA and flanking sequences is made. This DNA construct is transfected into pluripotent embryonic stem cells competent for recombination. The identical flanking sequences align with one another, and chromosomal recombination occurs in which the targeted sequence is replaced with the insert sequence, as described in Bradley, A., Production and Analysis of Chimeric Mice, in *Teratocarcinomas and Embryonic Stem Cells—A Practical Approach*, 1987, E. Roberson, Editor, IRC Press, pages 113–151. The stem cells are injected into an embryo, which is then implanted into a female animal and allowed to be born. The animals may contain germ cells derived from the injected stem cells, and subsequent matings may produce animals heterozygous and homozygous for the disrupted gene.

Transgenic non-human animals may also be useful for testing nucleic acid changes to identify additional mutations responsible for macular degeneration. A transgenic non-human animal may comprise a recombinant ABCR.

The present invention is also directed to gene therapy. For purposes of the present invention, gene therapy refers to the transfer and stable insertion of new genetic information into cells for the therapeutic treatment of diseases or disorders. A foreign sequence or gene is transferred into a cell that proliferates to spread the new sequence or gene throughout the cell population. Sequences include antisense sequence of all or part of ABCR, such as an antisense sequence to all or part of the sequences identified as SEQ ID NO: 1, 2, and 5. Known methods of gene transfer include microinjection, electroporation, liposomes, chromosome transfer, transfection techniques, calcium-precipitation transfection techniques, and the like. In the instant case, macular degeneration may result from a loss of gene function, as a result of a mutation for example, or a gain of gene function, as a result of an extra copy of a gene, such as three copies of a wild-type gene, or a gene over expressed as a result of a mutation in a promoter, for example. Expression may be altered by activating or deactivating regulatory elements, such as a promoter. A mutation may be corrected by replacing the mutated sequence with a wild-type sequence or inserting an antisense sequence to bind to an over expressed sequence or to a regulatory sequence.

Numerous techniques are known in the art for the introduction of foreign genes into cells and may be used to construct the recombinant cells for purposes of gene therapy, in accordance with this embodiment of the invention. The technique used should provide for the stable transfer of the heterologous gene sequence to the stem cell, so that the

heterologous gene sequence is heritable and expressible by stem cell progeny, and so that the necessary development and physiological functions of the recipient cells are not disrupted. Techniques which may be used include but are not limited to chromosome transfer (e.g., cell fusion, chromosome-mediated gene transfer, micro cell-mediated gene transfer), physical methods (e.g., transfection, spheroplast fusion, microinjection, electroporation, liposome carrier), viral vector transfer (e.g., recombinant DNA viruses, recombinant RNA viruses) and the like (described in Cline, M. J., 1985, Pharmac. Ther. 29:69–92, incorporated herein by reference in its entirety).

The term "purified", when used to describe the state of nucleic acid sequences of the invention, refers to nucleic acid sequences substantially free of nucleic acid not coding for ABCR or other materials normally associated with nucleic acid in non-recombinant cells, i.e., in its "native state."

The term "purified" or "in purified form" when used to describe the state of an ABCR nucleic acid, protein, polypeptide, or amino acid sequence, refers to sequences substantially free, to at least some degree, of cellular material or other material normally associated with it in its native state. Preferably the sequence has a purity (homogeneity) of at least about 25% to about 100%, More preferably the purity is at least about 50%, when purified in accordance with standard techniques known in the art.

In accordance with methods of the present invention, methods of detecting retinal or macular degenerations in a patient are provided comprising obtaining a patient tissue sample for testing. The tissue sample may be solid or liquid, a body fluid sample such as and not limited to blood, skin, serum, saliva, sputum, mucus, bone marrow, urine, lymph, and a tear; and feces. In addition, a tissue sample from amniotic fluid or chorion may be provided for the detection of retinal or macular degeneration in utero in accordance with the present invention.

A test fragment is defined herein as an amplified sample comprising ABCR-specific nucleic acids from a patient suspected of having retinal or macular degeneration. A control fragment is an amplified sample comprising normal or wild-type ABCR-specific nucleic acids from an individual not suspected of having retinal or macular degeneration.

The method of amplifying nucleic acids may be the polymerase chain reaction using a pair of primers wherein at least one primer within the pair is selected from the group consisting of SEQ ID NOS: 12–113. When the polymerase chain reaction is the amplification method of choice, a pair of primers may be used such that one primer of the pair is selected from the group consisting of SEQ ID NOS: 12–113.

Nucleic acids, such as DNA (such as and not limited to, genomic DNA and cDNA) and/or RNA (such as and not limited to mRNA) are obtained from the patient sample. Preferably RNA is obtained.

Nucleic acid extraction is followed by amplification of the same by any technique known in the art. The amplification step includes the use of at least one primer sequence which is complementary to a portion of ABCR-specific expressed nucleic acids or sequences on flanking intronic genomic sequences in order to amplify exon or coding sequences. Primer sequences useful in the amplification methods include and are not limited to SEQ ID NOS: 12–113, which may be used in the amplification methods. Any primer sequence of about 10 nucleotides to about 35 nucleotides, more preferably about 15 nucleotides to about 30 nucleotides, even more preferably about 17 nucleotides to about 25 nucleotides may be useful in the amplification step of the methods of the present invention. In addition, mismatches within the sequences identified above, which achieve the methods of the invention, such that the mismatched sequences are substantially complementary and thus hybridizable to the sequence sought to be identified, are also considered within the scope of the disclosure. Mismatches which permit substantial similarity to SEQ ID NOS: 12–113, such as and not limited to sequences with similar hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. The primers may also be unmodified or modified. Primers may be prepared by any method known in the art such as by standard phosphoramidite chemistry. See Sambrook et al., supra.

The method of amplifying nucleic acids may be the polymerase chain reaction using a pair of primers wherein at least one primer within the pair is selected from the group consisting of SEQ ID NOS: 12–113. When the polymerase chain reaction is the amplification method of choice, a pair of primers may be used such that one primer of the pair is selected from the group consisting of SEQ ID NOS: 12–113.

When an amplification method includes the use of two primers, a first primer and a second primer, such as in the polymerase chain reaction, one of the first primer or second primer may be selected from the group consisting of SEQ ID NOS: 12–113. Any primer pairs which copy and amplify nucleic acids between the pairs pointed toward each other and which are specific for ABCR may be used in accordance with the methods of the present invention.

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR) which is described in detail in U.S. Pat. Nos. 4,683,195, 4,683,202 and 4,800,159, and in Innis et al., *PCR Protocols*, Academic Press, Inc., San Diego Calif., 1990, each of which is incorporated herein by reference in its entirety. Briefly, in PCR, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase (e.g., Taq polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction products and the process is repeated. Alternatively, a reverse transcriptase PCR amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in EPA No.320,308, incorporated herein by reference in its entirety. In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Pat. No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Application No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA which has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence which can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[alpha-thio]triphosphates in one strand of a restriction site (Walker, G. T., et al., *Proc. Natl. Acad, Sci.* (*U.S.A*) 1992, 89:392–396, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, i.e. nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and which involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

ABCR-specific nucleic acids can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-ABCR specific DNA and middle sequence of ABCR specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe identified as distinctive products, generate a signal which is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a ABCR-specific expressed nucleic acid.

Still other amplification methods described in GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes are added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh D., et al., *Proc. Natl. Acad. Sci*. (*U.S.A.*) 1989, 86:1173, Gingeras T. R., et al., PCT Application WO 88/10315, each of which is incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a clinical sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer which has ABCR-specific sequences. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat denatured again. In either case the single stranded DNA is made fully double stranded by addition of second ABCR-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into double stranded DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate ABCR-specific sequences.

Davey, C., et al., European Patent Application Publication No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA ("dsDNA") which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA: RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

Miller, H. I., et al., PCT application WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; i.e. new templates are not produced from the resultant RNA transcripts. Other amplification methods include "race" disclosed by Frohman, M. A., In: *PCR Protocols: A Guide to Methods and Applications* 1990, Academic Press, N.Y.) and "one-sided PCR" (Ohara, O., et al., *Proc. Natl. Acad. Sci.* (*U.S.A*) 1989, 86:5673–5677), all references herein incorporated by reference in their entirety.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu, D. Y. et al., *Genomics* 1989, 4:560, incorporated herein by reference in its entirety), may also be used in the amplification step of the present invention.

Test fragment and control fragment may be amplified by any amplification methods known to those of skill in the art, including and not limited to the amplification methods set forth above. For purposes of the present invention, amplification of sequences encoding patient and wild-type ABCR includes amplification of a portion of a sequence such as and not limited to a portion of an ABCR sequence of SEQ ID NO: 1, such as sequence of a length of about 10 nucleotides to about 1,000 nucleotides, more preferably about 10 nucleotides to about 100 nucleotides, or having at least 10

nucleotides occurring anywhere within the SEQ ID NO: 1, where sequence differences are known to occur within ABCR test fragments. Thus, for example, a portion of the sequence encoding ABCR of a patient sample and a control sample may be amplified to detect sequence differences between these two sequences.

Following amplification of the test fragment and control fragment, comparison between the amplification products of the test fragment and control fragment is carried out. Sequence changes such as and not limited to nucleic acid transition, transversion, and restriction digest pattern alterations may be detected by comparison of the test fragment with the control fragment.

Alternatively, the presence or absence of the amplification product may be detected. The nucleic acids are fragmented into varying sizes of discrete fragments. For example, DNA fragments may be separated according to molecular weight by methods such as and not limited to electrophoresis through an agarose gel matrix. The gels are then analyzed by Southern hybridization. Briefly, DNA in the gel is transferred to a hybridization substrate or matrix such as and not limited to a nitrocellulose sheet and a nylon membrane. A labeled probe encoding an ABCR mutation is applied to the matrix under selected hybridization conditions so as to hybridize with complementary DNA localized on the matrix. The probe may be of a length capable of forming a stable duplex. The probe may have a size range of about 200 to about 10,000 nucleotides in length, preferably about 500 nucleotides in length, and more preferably about 2,454 nucleotides in length. Mismatches which permit substantial similarity to the probe, such as and not limited to sequences with similar hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. Various labels for visualization or detection are known to those of skill in the art, such as and not limited to fluorescent staining, ethidium bromide staining for example, avidin/biotin, radioactive labeling such as ^{32}P labeling, and the like. Preferably, the product, such as the PCR product, may be run on an agarose gel and visualized using a stain such as ethidium bromide. See Sambrook et al., supra. The matrix may then be analyzed by autoradiography to locate particular fragments which hybridize to the probe. Yet another alternative is the sequencing of the test fragment and the control fragment to identify sequence differences. Methods of nucleic acid sequencing are known to those of skill in the art, including and not limited to the methods of Maxam and Gilbert, *Proc. Natl. Acad. Sci., USA* 1977, 74, 560–564 and Sanger, *Proc. Natl. Acad. Sci., USA* 1977, 74, 5463–5467.

A pharmaceutical composition comprising all or part of a sequence for ABCR may be delivered to a patient suspected of having retinal or macular degeneration. The sequence may be an antisense sequence. The composition of the present invention may be administered alone or may generally be administered in admixture with a pharmaceutical carrier. The pharmaceutically-acceptable carrier may be selected with regard to the intended route of administration and the standard pharmaceutical practice. The dosage will be about that of the sequence alone and will be set with regard to weight, and clinical condition of the patient. The proportional ratio of active ingredient to carrier will naturally depend, inter alia, on the chemical nature, solubility, and stability of the sequence, as well as the dosage contemplated.

The sequences of the invention may be employed in the method of the invention singly or in combination with other compounds, including and not limited to other sequences set forth in the present invention. The method of the invention may also be used in conjunction with other treatments such as and not limited to antibodies, for example. For in vivo applications the amount to be administered will also depend on such factors as the age, weight, and clinical condition of the patient. The composition of the present invention may be administered by any suitable route, including as an eye drop, inoculation and injection, for example, intravenous, intraocular, oral, intraperitoneal, intramuscular, subcutaneous, topically, and by absorption through epithelial or mucocutaneous linings, for example, conjunctival, nasal, oral, vaginal, rectal and gastrointestinal.

The mode of administration of the composition may determine the sites in the organism to which the compound will be delivered. For instance, topical application may be administered in creams, ointments, gels, oils, emulsions, pastes, lotions, and the like. For parenteral administration, the composition maybe used in the form of sterile aqueous or non-aqueous solution which may contain another solute, for example, sufficient salts, glucose or dextrose to make the solution isotonic. A non-aqueous solution may be comprise an oil, for example. For oral mode of administration, the present invention may be used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and suspension, and the like. Various disintegrants, such as starch, and lubricating agents may be used. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, certain sweetening and/or flavoring agents may be added.

A diagnostic kit for detecting retinal or macular degeneration comprising in one or more containers at least one primer which is complementary to an ABCR sequence and a means for visualizing amplified DNA is also within the scope of the present invention. Alternatively, the kit may comprise two primers. In either case, the primers may be selected from the group consisting of SEQ ID NOS: 12–113, for example. The diagnostic kit may comprise a pair of primers wherein one primer within said pair is complementary to a region of the ABCR gene, wherein one of said pair of primers is selected from the group consisting of SEQ ID NO: 12–113, a probe specific to the amplified product, and a means for visualizing amplified DNA, and optionally including one or more size markers, and positive and negative controls. The diagnostic kit of the present invention may comprise one or more of a fluorescent dye such as ethidium bromide stain, ^{32}p, and biotin, as a means for visualizing or detecting amplified DNA. Optionally the kit may include one or more size markers, positive and negative controls, restriction enzymes, and/or a probe specific to the amplified product.

The following examples are illustrative but are not meant to be limiting of the invention.

EXAMPLES

Identification of the ABCR as a Candidate Gene for STGD

One of the 21 new human genes from the ABC superfamily, hereafter called ABCR (retina-specific ABC transporter), was identified (Allikmets et al. 1996) among expressed sequence tags (ESTs) obtained from 5,000 human retina cDNA clones (Wang, Y., Macke, J. P., Abella, B. S., Andreasson, K., Worley, P., Gilbert, D. J., Copeland, N. G., Jenkins, N. A., and Nathans, J. (1996)) and among ESTs obtained from human retina cDNA clones by the I.M.A.G.E. consortium (Lennon et al., 1996). ABCR is closely related to

the previously described mouse and human ABC1 and ABC2 genes (Luciani et al., 1994; Allikmets et al., 1995). To determine whether ABCR might cause a disease, the gene was mapped with a whole genome radiation hybrid panel (GeneBridge 4; Research Genetics, Huntsville, Ala.). ABCR mapped to the human chromosome 1p13-p21 region, close to microsatellite markers D1S236 and D1S188. To define further the location of the gene, PCR primers, 3'UTR-For 5'ATCCTCTGACTCAGCAATCACA, SEQ ID NO: 7, and 3'UTR-Rev 5'TTGCAATTACAAATGCAATGG, SEQ ID NO: 8, from the putative 3' untranslated region were used to screen YACs from the previously described contig between these anonymous markers (Anderson et al., 1995). At least 12 YACs contain the 3' end of the ABCR gene, including 924_e__9, 759_d__7, 775_c__2, 782_b__4, 982_g__5, 775_b__2, 765_a__3, 751_f__2, 848_e__3, 943_h__8, 934_g__7, and 944_b__12 (FIG. **1**). These YACs delineate a region containing the STGD gene between markers D1S3361 and D1S236 (Anderson et al., 1995).

Expression of the ABCR Gene

Additional support suggesting that ABCR is a candidate STGD gene came from expression studies and inspection of the EST databases.

Searches of the dbEST (Boguski et al., 1993) database were performed with BLAST on the NCBI file server (Altschul et al., 1990). Amino acid alignments were generated with PILEUP (Feng and Doolittle, 1987). Sequences were analyzed with programs of the Genetics Computer Group package (Devereaux et al., 1984) on a VAX computer.

Clones corresponding to the mouse ortholog of the human ABCR gene were isolated from the mouse retina cDNA library and end-sequenced. The chromosomal location of the mouse ABCR gene was determined on The Jackson Laboratory (Bar Harbor, Me.) interspecific backcross mapping panel (C57BL/6JEi×SPRET/Ei)F1×SPRET/Ei (Rowe et al., 1994) known as Jackson BSS. Mapping was performed by SSCP analysis with the primers MABCR1F 5'ATC CAT ACC CTT CCC ACT CC, SEQ ID NO: 9, and MABCR1R 5' GCA GCA GAA GAT AAG CAC ACC, SEQ ID NO. 10. The allele pattern of the Abcr was compared to the 250 other loci mapped previously in the Jackson BSS cross (http://www.jax.org).

DNA fragments used as probes were purified on a 1% low-melting temperature agarose gel. The probe sequences are set forth within the genomic sequence of SEQ ID NO: 1 and FIG. **3**. DNA was labeled directly in agarose with the Random Primed DNA Labeling Kit (Boehringer Mannheim, Indianapolis, Ind.) and hybridized to multiple tissue Northern blot and a Master blot (Clontech, Palo Alto, Calif.), according to the manufacturer's instructions. Each blot contained 2 μg of poly A^+ RNA from various human tissues. Total RNA was isolated from adult rat tissues using the guanidinium thiocyanate method (Chomczynski and Saachi, 1987) and resolved by agarose gel electrophoresis in the presence of formaldehyde (Sambrook et al., 1989). Hybridization with the mouse ABCR probe was performed in 50% formamide, 5×SSC at 42° C., and filters were washed in 0.1×SSC at 68° C.

Hybridization of a 3' ABCR cDNA probe to a multiple tissue Northern blot and a MasterBlot (Clontech, Palo Alto, Calif.) indicated that the gene was not expressed detectably in any of the 50 non-retinal fetal and adult tissues examined, consistent with the observation that all 12 of the ABCR clones in the EST database originated from retinal cDNA libraries. Furthermore, screening cDNA libraries from both developing mouse eye and adult human retina with ABCR probes revealed an estimated at 0.1%–1% frequency of ABCR clones of all cDNA clones in the library. Hybridization of the ABCR probe to a Northern blot containing total RNA from rat retina and other tissues showed that the expression of this gene is uniquely retina-specific (FIG. **2**). The transcript size is estimated to be 8 kb.

Sequence and Exon/Intron Structure of the ABCR cDNA

Several ESTs that were derived from retina cDNA libraries and had high similarity to the mouse Abc1 gene were used to facilitate the assembly of most of the ABCR cDNA sequence. Retina cDNA clones were linked by RT-PCR, and repetitive screening of a human retina cDNA library with 3' and 5' PCR probes together with 5' RACE were used to characterize the terminal sequences of the gene.

cDNA clones containing ABCR sequences were obtained from a human retina cDNA library (Nathans et al., 1986) and sequenced fully. Primers were designed from the sequences of cDNA clones from 5' and 3' regions of the gene and used to link the identified cDNA clones by RT-PCR with retina QUICK-Clone cDNA (Clontech, Palo Alto, Calif.) as a template. PCR products were cloned into pGEM®-T vector (Promega, Madison, Wis.). Mouse ABCR cDNA clones were obtained from screening a developing mouse eye cDNA library (H. Sun, A. Lanahan, and J. Nathans, unpublished). The pGEM®-T Vector is prepared by cutting pGEM®-5Zf(+) DNA with EcoR V and adding to a 3' terminal thymidine to both ends. These single 3'-T overhangs at the insertion site greatly improve the efficiency of ligation of PCR products because of the nontemplate-dependent addition of a single deoxyadenosine (A) to the 3'-ends of PCR products by many thermostable polymerases. The pGEM®-5Zf(+) Vector contains the origin of replication of the filamentous phage f1 and can be used to produce ssDNA. The plasmid also contains T7 and SP6 RNA polymerase promoters flanking a multiple cloning region within the α-peptide coding region for the enzyme β-galactosidase. Insertional inactivation of the α-peptide allows recombinant clones to be identified directly by color screening on indicator plates. cDNA clones from various regions of the ABCR gene were used as probes to screen a human genomic library in Lambda FIX II (#946203, Stratagene, LaJolla, Calif.). Overlapping phage clones were mapped by EcoRI and BamHI digestion. A total of 6.9 kb of the ABCR sequence was assembled, (FIG. **3**) resulting in a 6540 bp (2180 amino acid) open reading frame.

Screening of a bacteriophage lambda human genomic library with cDNA probes yielded a contig that spans approximately 100 kb and contains the majority of the ABCR coding region. The exon/intron structure of all fifty one exons of the gene were characterized by direct sequencing of genomic and cDNA clones. Intron sizes were estimated from the sizes of PCR products using primers from adjacent exons with genomic phage clones as templates.

Primers for the cDNA sequences of the ABCR were designed with the PRIMER program (Lincoln et al., 1991). Both ABCR cDNA clones and genomic clones became templates for sequencing. Sequencing was performed with the Taq Dyedeoxy Terminator Cycle Sequencing kit (Applied Biosystems, Foster City, Calif.), according to the manufacturer's instructions. Sequencing reactions were resolved on an ABI 373A automated sequencer. Positions of introns were determined by comparison between genomic and cDNA sequences. Primers for amplification of individual exons were designed from adjacent intron sequences 20–50 bp from the splice site and are set forth in Table 1.

TABLE 1

Exon/intron Primers for ABCR

PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON1:F	ACCCTCTGCTAAGCTCAGAG	12
ABCR.EXON1:R	ACCCCACACTTCCAACCTG	13
ABCR.EXON2:F	AAGTCCTACTGCACACATGG	14
ABCR.EXON2:R	ACACTCCCACCCCAAGATC	15
ABCR.EXON3:F	TTCCCAAAAAGGCCAACTC	16
ABCR.EXON3:R	CACGCACGTGTGCATTCAG	17
ABCR.EXON4:F	GCTATTTCCTTATTAATGAGGC	18
ABCR.EXON4:R	CCAACTCTCCCTGTTCTTTC	19
ABCR.EXON5:F	TGTTTTCCAATCGACTCTGGC	20
ABCR.EXON5:R	TTCTTGCCTTTCTCAGGCTGG	21
ABCR.EXON6:F	GTATTCCCAGGTTCTGTGG	22
ABCR.EXON6:R	TACCCCAGGAATCACCTTG	23
ABCR.EXON7:F	AGCATATAGGAGATCAGACTG	24
ABCR.EXON7:R	TGACATAAGTGGGGTAAATGG	25
ABCR.EXON8:F	GAGCATTGGCCTCACAGCAG	26
ABCR.EXON8:R	CCCCAGGTTTGTTTCACC	27
ABCR.EXON9:F	AGACATGTGATGTGGATACAC	28
ABCR.EXON9:R	GTGGGAGGTCCAGGGTACAC	29
ABCR.EXON10:F	AGGGGCAGAAAAGACACAC	30
ABCR.EXON10:R	TAGCGATTAACTCTTTCCTGG	31
ABCR.EXON11:F	CTCTTCAGGGAGCCTTAGC	32
ABCR.EXON11:R	TTCAAGACCACTTGACTTGC	33
ABCR.EXON12:F	TGGGACAGCAGCCTTATC	34
ABCR.EXON12:R	CCAAATGTAATTTCCCACTGAC	35
ABCR.EXON13:F	AATGAGTTCCGAGTCACCCTG	36
ABCR.EXON13:R	CCCATTCGCGTGTCATGG	37
ABCR.EXON14:F	TCCATCTGGGCTTTGTTCTC	38
ABCR.EXON14:R	AATCCAGGCACATGAACAGG	39
ABCR.EXON15:F	AGGCTGGTGGGAGAGAGC	40
ABCR.EXON15:R	AGTGGACCCCCTCAGAGG	41
ABCR.EXON16:F	CTGTTGCATTGGATAAAAGGC	42
ABCR.EXON16:R	GATGAATGGAGAGGGCTGG	43
ABCR.EXON17:F	CTGCGGTAAGGTAGGATAGGG	44
ABCR.EXON17:R	CACACCGTTTACATAGAGGGC	45
ABCR.EXON18:F	CCTCTCCCCTCCTTTCCTG	46
ABCR.EXON18:R	GTCAGTTTCCGTAGGCTTC	47
ABCR.EXON19:F	TGGGGCCATGTAATTAGGC	48

TABLE 1-continued

Exon/intron Primers for ABCR

PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON19:R	TGGGAAAGAGTAGACAGCCG	49
ABCR.EXON20:F	ACTGAACCTGGTGTGGGG	50
ABCR.EXON20:R	TATCTCTGCCTGTGCCCAG	51
ABCR.EXON21:F	GTAAGATCAGCTGCTGGAAG	52
ABCR.EXON21:R	GAAGCTCTCCTGCACCAAGC	53
ABCR.EXON22:F	AGGTACCCCCACAATGCC	54
ABCR.EXON22:R	TCATTGTGGTTCCAGTACTCAG	55
ABCR.EXON23:F	TTTTTGCAACTATATAGCCAGG	56
ABCR.EXON23:R	AGCCTGTGTGAGTAGCCATG	57
ABCR.EXON24:F	GCATCAGGGCGAGGCTGTC	58
ABCR.EXON24:R	CCCAGCAATACTGGGAGATG	59
ABCR.EXON25:F	GGTAACCTCACAGTCTTCC	60
ABCR.EXON25:R	GGGAACGATGGCTTTTTGC	61
ABCR.EXON26:F	TCCCATTATGAAGCAATACC	62
ABCR.EXON26:R	CCTTAGACTTTCGAGATGG	63
ABCR.EXON27:F	GCTACCAGCCTGGTATTTCATTG	64
ABCR.EXON27:R	GTTATAACCCATGCCTGAAG	65
ABCR.EXON28:F	TGCACGCGCACGTGTGAC	66
ABCR.EXON28:R	TGAAGGTCCCAGTGAAGTGGG	67
ABCR.EXON29:F	CAGCAGCTATCCAGTAAAGG	68
ABCR.EXON29:R	AACGCCTGCCATCTTGAAC	69
ABCR.EXON30:F	GTTGGGCACAATTCTTATGC	70
ABCR.EXON30:R	GTTGTTTGGAGGTCAGGTAC	71
ABCR.EXON31:F	AACATCACCCAGCTGTTCCAG	72
ABCR.EXON31:R	ACTCAGGAGATACCAGGGAC	73
ABCR.EXON32:F	GGAAGACAACAAGCAGTTTCAC	74
ABCR.EXON32:R	ATCTACTGCCCTGATCATAC	75
ABCR.EXON33:F	AAGACTGAGACTTCAGTCTTC	76
ABCR.EXON33:R	GGTGTGCCTTTTAAAAGTGTGC	77
ABCR.EXON34:F	TTCATGTTTCCCTACAAAACCC	78
ABCR.EXON34:R	CATGAGAGTTTCTCATTCATGG	79
ABCR.EXON35:F	TGTTTACATGGTTTTTAGGGCC	80
ABCR.EXON35:R	TTCAGCAGGAGGAGGGATG	81
ABCR.EXON36:F	CCTTTCCTTCACTGATTTCTGC	82
ABCR.EXON36:R	AATCAGCACTTCGCGGTG	83
ABCR.EXON37:F	TGTAAGGCCTTCCCAAAGC	84
ABCR.EXON37:R	TGGTCCTTCAGCGCACACAC	85

TABLE 1-continued

Exon/intron Primers for ABCR

PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON38:F	CATTTTGCAGAGCTGGCAGC	86
ABCR.EXON38:R	CTTCTGTCAGGAGATGATCC	87
ABCR.EXON39:F	GGAGTGCATTATATCCAGACG	88
ABCR.EXON39:R	CCTGGCTCTGCTTGACCAAC	89
ABCR.EXON40:F	TGCTGTCCTGTGAGAGCATC	90
ABCR.EXON40:R	GTAACCCTCCCAGCTTTGG	91
ABCR.EXON41:F	CAGTTCCCACATAAGGCCTG	92
ABCR.EXON41:R	CAGTTCTGGATGCCCTGAG	93
ABCR.EXON42:F	GAAGAGAGGTCCCATGGAAAGG	94
ABCR.EXON42:R	GCTTGCATAAGCATATCAATTG	95
ABCR.EXON43:F	CTCCTAAACCATCCTTTGCTC	96
ABCR.EXON43:R	AGGCAGGCACAAGAGCTG	97
ABCR.EXON44:F	CTTACCCTGGGGCCTGAC	98
ABCR.EXON44:R	CTCAGAGCCACCCTACTATAG	99
ABCR.EXON45:F	GAAGCTTCTCCAGCCCTAGC	100
ABCR.EXON45:R	TGCACTCTCATGAAACAGGC	101
ABCR.EXON46:F	GTTTGGGGTGTTTGCTTGTC	102
ABCR.EXON46:R	ACCTCTTTCCCCAACCCAGAG	103
ABCR.EXON47:F	GAAGCAGTAATCAGAAGGGC	104
ABCR.EXON47:R	GCCTCACATTCTTCCATGCTG	105
ABCR.EXON48:F	TCACATCCCACAGGCAAGAG	106
ABCR.EXON48:R	TTCCAAGTGTCAATGGAGAAC	107
ABCR.EXON49:F	ATTACCTTAGGCCCAACCAC	108
ABCR.EXON49:R	ACACTGGGTGTTCTGGACC	109
ABCR.EXON50:F	GTGTAGGGTGGTGTTTTCC	110
ABCR.EXON50:R	AAGCCCAGTGAACCAGCTGG	111
ABCR.EXON51:F	TCAGCTGAGTGCCCTTCAG	112
ABCR.EXON51:R	AGGTGAGCAAGTCAGTTTCGG	113

In Table 1, "F" indicates forward, i.e., 5' to 3', "R" indicates reverse, i.e., 3' to 5'. PCR conditions were 95° C. for 8 minutes; 5 cycles at 62° C. for 20 seconds, 72° C. for 30 seconds; 35 cycles at 60° C. for 20 seconds, 72° C. for 30 seconds; 72° C. for 5 minutes (except that[a] was performed at 94°C. for 5 minutes); 5 cycles at 94° C. for 40 seconds; 60° C. for 30 seconds; 72° C. for 20 seconds; 35 cycles at 94 C. for 40 seconds; 56° C. for 30 seconds; 72° C. for 20 seconds, and 72° C. for 5 minutes.

Amplification of exons was performed with AmpliTaq Gold polymerase in a 25 μl volume in 1×PCR buffer supplied by the manufacturer (Perkin Elmer, Foster City, Calif.). Samples were heated to 95° C. for 10 minutes and amplified for 35–40 cycles at 96° C. for 20 seconds; 58° C. for 30 seconds; and 72° C. for 30 seconds. PCR products were analyzed on 1–1.5% agarose gels and in some cases digested with an appropriate restriction enzymes to verify their sequence. Primer sequences and specific reaction conditions are set forth in Table 1. The sequence of the ABCR cDNA has been deposited with GenBank under accession # U88667.

Homology to ABC Superfamily Members

A BLAST search revealed that ABCR is most closely related to the previously characterized mouse Abc1 and Abc2 genes (Luciani et al., 1994) and to another human gene (ABCC) which maps to chromosome 16p13.3 (Klugbauer and Hofinann, 1996). These genes, together with ABCR and a gene from *C. elegans* (GenBank #Z29117), form a subfamily of genes specific to multicellular organisms and not represented in yeast (Michaelis and Berkower, 1995; Allikmets et al., 1996). Alignment of the CDNA sequence of ABCR with the Abc1, Abc2, and ABCC genes revealed, as expected, the highest degree of homology within the ATP-binding cassettes. The predicted amino acid identity of the ABCR gene to mouse Abc1 was 70% within the ATP-binding domains; even within hydrophobic membrane-spanning segments, homology ranged between 55 and 85% (FIG. **4**). The putative ABCR initiator methionine shown in FIGS. **3** and **4** corresponds to a methionine codon at the 5' end of Abc1 (Luciani et al., 1994).

ABCR shows the composition of a typical full-length ABC transporter that consists of two transmembrane domains (TM), each with six membrane spanning hydrophobic segments, as predicted by a hydropathy plot (data not shown), and two highly conserved ATP-binding domains (FIGS. **3** and **4**). In addition, the HH1 hydrophobic domain, located between the first ATP and second TM domain and specific to this subfamily (Luciani et al., 1994), showed a predicted 57% amino acid identity (24 of 42 amino acids) with the mouse Abc1 gene.

To characterize the mouse ortholog of ABCR, cDNA clones from a developing mouse eye library were isolated. A partial sequence of the mouse cDNA was utilized to design PCR primers to map the mouse Abcr gene in an interspecific backcross mapping panel (Jackson BSS). The allele pattern of Abcr was compared to 2450 other loci mapped previously in the Jackson BSS cross; linkage was found to the distal end of chromosome 3 (FIG. **5**). No recombinants were observed between Abcr and D13Mit13. This region of the mouse genome is syntenic with human chromosome 1p13-p21. Thus far, no eye disease phenotype has been mapped to this region of mouse chromosome 3.

Compound Heterozygous and Homozygous Mutations in STGD Patients

One hundred forty-five North American and three Saudi Arabian families with STGD/FFM were examined. Among these, at least four were consanguineous families in which the parents were first cousins. Entry criteria for the characterization of the clinical and angiographic diagnosis of Stargardt disease, ascertainment of the families, and methodology for their collection, including the consanguineous families from Saudi Arabia, were as provided in Anderson et al., 1995; and Anderson, 1996.

Mutational analysis of the ABCR gene was pursued in the above identified one hundred forty-eight STGD families previously ascertained by strict definitional criteria and shown to be linked to chromosome 1p (Anderson et al., 1995; Anderson, 1996). To date, all 51 exons have been used for mutation analysis.

Mutations were detected by a combined SSCP (Orita et al., 1989) and heteroduplex analysis (White et al., 1992)

under optimized conditions (Glavč and Dean, 1993). Genomic DNA samples (50 ng) were amplified with AmpliTaq Gold polymerase in 1×PCR buffer supplied by the manufacturer (Perkin Elmer, Foster City, Calif.) containing [α-^{32}P] dCTP. Samples were heated to 95° C. for 10 minutes and amplified for 35–40 cycles at 96° C. for 20 seconds; 58° C. for 30 seconds; and 72° C. for 30 seconds. Products were diluted in 1:3 stop solution, denatured at 95° C. for 5 minutes, chilled in ice for 5 minutes, and loaded on gels. Gel formulations include 6% acrylamide:Bis (2.6% cross-linking), 10% glycerol at room temperature, 12 W; and 10% acrylamide:Bis (1.5% cross-linking), at 4° C., 70 W. Gels were run for 2–16 hours (3000 Vh/100 bp), dried, and exposed to X-ray film for 2–12 hours. Some exons were analyzed by SSCP with MDE acrylamide (FMC Bioproducts, Rockland, Me.) with and without 10% glycerol for 18 hours, 4 watts at room temperature with α-P^{32}-dCTP labeled DNA. Heteroduplexes were identified from the double-stranded DNA at the bottom of the gels, and SSCPs were identified from the single-stranded region. Samples showing variation were compared with other family members to assess segregation of the alleles and with at least 40 unrelated control samples, from either Caucasian or Saudi Arabian populations, to distinguish mutations from polymorphisms unrelated to STGD. PCR products with SSCP or heteroduplex variants were obtained in a 25 μl volume, separated on a 1% agarose gel, and isolated by a DNA purification kit (PGC Scientific, Frederick, Md.). Sequencing was performed on an ABI sequencer with both dye primer and dye terminator chemistry.

Some mutations were identified with a heteroduplex analysis protocol (Roa et al., 1993). Equimolar amounts of control and patient PCR products were mixed in 0.2 ml tubes. Two volumes of PCR product from a normal individual served as a negative control, and MPZ exon 3 from patient BAB731 as a positive control (Roa et al., 1996). Samples were denatured at 95 ° C. for 2 minutes and cooled to 35° C. at a rate of 1° C./minute. Samples were loaded onto 1.0 mm thick, 40 cm MDE gels (FMC Bioproducts, Rockland, Me.), electrophoresed at 600–800 V for 15–20 hours, and visualized with ethidium bromide. Samples showing a variant band were reamplified with biotinylated forward and reverse primers and immobilized on streptavidin-conjugated beads (Warner et al. 1996). The resulting single strands were sequenced by the dideoxy-sequencing method with Sequenase 2.0 (Amersham, Arlington Heights, Ill.).

A total of seventy five mutations were identified, the majority representing missense mutations in conserved amino acid positions. However, several insertions and deletions representing frameshifts were also found (Table 2). Two missense alterations (D847H, R943Q) were found in at least one control individual, suggesting that they are neutral polymorphisms. The remaining mutations were found in patients having macular degeneration and were not found in at least 220 unrelated normal controls (440 chromosomes), consistent with the interpretation that these alterations represent disease-causing mutations, not polymorphisms. One of the mutations, 5892+1 G→T, occurs in family AR144 in which one of the affected children is recombinant for the flanking marker D1S236 (Anderson et al., 1995). This mutation, however, is present in the father as well as in both affected children. Therefore, the ABCR gene is non-recombinant with respect to the Stargardt disease locus.

The mutations are scattered throughout the coding sequence of the ABCR gene (see Table 2 and FIGS. **3**A–H), although clustering within the conserved regions of the ATP-binding domains is noticeable. Homozygous mutations were detected in three likely consanguineous families, two Saudi Arabian and one North American (Anderson et al., 1995), in each of which only the affected individuals inherited the identical disease allele (Table 2; FIG. **6**). Forty two compound heterozygous families were identified in which the two disease alleles were transmitted from different parents to only the affected offspring (Table 2).

TABLE 2

Mutations in the ABCR gene in STGD Families

Nucleotide	Amino Acid	#Families		Exon
0223T->G	C75G	1		3
0634C->T	R212C	1	6	
0664del13	fs	1		6
0746A->G	D249G	1	6	
1018T->G	Y340D	2	8	
1411G->A	E471K	1	11	
1569T->G	D523E	1	12	
1715G->A	R572Q	2	12	
1715G->C	R572P	1	12	
1804C->T	R602W	1		13
1822T->A	F608I	1		13
1917C->A	Y639X	1	13	
2453G->A	G818E	1	16	
2461T->A	W821R	1		16
2536G->C	D846H	1	16	
2588G->C	G863A	11	17	
2791G->A	V931M	1		19
2827C->T	R943W	1		19
2884delC	fs	1		19
2894A->G	N965S	3	19	
3083C->T	A1028V	14		21
3211delGT	fs	1		22
3212C->T	S1071L	1		22
3215T->C	V1072A	1		22
3259G->A	E1087K	1		22
3322C->T	R1108C	6		22
3364G->A	E1122K	1		23
3385G->T	R1129C	1		23
3386G->T	R1129L	1		23
3602T->G	L1201R	1		24
3610G->A	D1204N	1		25
4139C->T	P1380L	2		28
4195G->A	E1399K	1		28
4222T->C	W1408R	3		28
4232insTATG	fs	1	28	
4253+5G->T	splice	1	28	
4297G->A	V1433I	1		29
4316G->A	G1439D	1		29
4319T->C	F1440S	1		29
4346G->A	W1449X	1		29
4462T->C	C1488R	1		30
4469G->A	C1490Y	1		31
4577C->T	T1526M	6		32
4594G->A	D1532N	2		32
4947delC	fs	1		36
5041del15	VVAIC1681del	1		37
5196+2T->C	splice	1	37	
5281del9	PAL1761del	1		38
5459G->C	R1820P	1		39
5512C->T	H1838Y	1		40
5527C->T	R1843W	1		40
5585+1G->A	splice	1	41	
5657G->A	G1886E	1		41
5693G->A	R1898H	4		41
5714+5G->A	splice	8	41	
5882G->A	G1961E	16		43
5898+1G->A	splice	3	43	
5908C->T	L1970F	1		44
5929G->A	G1977S	1		44
6005+1G->T	splice	1	44	
6079C->T	L2027F	11		45
6088C->T	R2030X	1		45
6089G->A	R2030Q	1		45
6112C->T	R2038W	1		45
6148G->C	V2050L	2		46
6166A->T	K2056X	1		46

TABLE 2-continued

Mutations in the ABCR gene in STGD Families

Nucleotide	Amino Acid	#Families	Exon
6229C->T	R2077W	1	46
6286G->A	E2096K	1	47
6316C->T	R2106C	1	47
6391G->A	E2131K	1	48
6415C->T	R2139W	1	48
6445C->T	R2149X	1	48
6543del36	1181del12	1	49
6709delG	fs	1	49

Mutations are named according to standard nomenclature. The column headed "Exon" denotes which of the 51 exons of ABCR contain the mutation. The column headed "# Families" denotes the number of Stargardt families which displayed the mutation. The column headed "Nucleotide" gives the base number starting from the A in the initiator ATG, followed by the wild type sequence and an arrow indicating the base it is changed to; del indicates a deletion of selected bases at the given position in the ABCR gene; ins indicates an insertion of selected bases at the given position; splice donor site mutations are indicated by the number of the last base of the given exon, followed by a plus sign and the number of bases into the intron where the mutation occurs. The column headed "Amino Acid" denotes the amino acid change a given mutation causes; fs indicates a frameshift mutation leading to a truncated protein; splice indicates a splice donor site mutation; del indicates an in-frame deletion of the given amino acids.

Mutations are named according to standard nomenclature. Exon numbering according to the nucleotide position starting from the A in the initiator ATG.

In Situ Hybridization

STGD is characterized histologically by a massive accumulation of a lipofuscin-like substance in the retinal pigment epithelium (RPE). This characteristic has led to the suggestion that STGD represents an RPE storage disorder (Blacharski et al., 1988). It was therefore of interest that ABCR transcripts were found to be abundant in the retina. To identify the site(s) of ABCR gene expression at higher resolution and to determine whether the gene is also expressed in the RPE, the distribution of ABCR transcripts was visualized by in situ hybridization to mouse, rat, bovine, and macaque ocular tissues.

In situ hybridization with digoxigenin-labeled riboprobes was performed as described by Schaeren-Wiemers and Gerfin-Moser, 1993. For mouse and rat, unfixed whole eyes were frozen and sectioned; macaque retinas were obtained following cardiac perfusion with paraformaldehyde as described (Zhou et al., 1996). An extra incubation of 30 min in 1% Triton X-100, 1×PBS was applied to the fixed monkey retina sections immediately after the acetylation step. The templates for probe synthesis were: (1) a 1.6 kb fragment encompassing the 3' end of the mouse Abcr coding region, (2) a full length cDNA clone encoding the mouse blue cone pigment (Chiu et al., 1994), and (3) a macaque rhodopsin coding region segment encoding residues 133 to 254 (Nickells, R. W., Burgoyne, C. F., Quigley, H. A., and Zack, D. J. (1995)).

This analysis showed that ABCR transcripts are present exclusively within photoreceptor cells (FIG. **7**). ABCR transcripts are localized principally to the rod inner segments, a distribution that closely matches that of rhodopsin gene transcripts. Interestingly, ABCR hybridization was not observed at detectable levels in cone photoreceptors, as judged by comparisons with the hybridization patterns obtained with a blue cone pigment probe (compare FIG. **7**A and FIG. **7**D, FIG. **7**E with FIG. **7**F and FIG. **7**G with FIG. **7**H). Because melanin granules might obscure a weak hybridization signal in the RPE of a pigmented animal, the distribution of ABCR transcripts was also examined in both albino rats and albino mice. In these experiments, the ABCR hybridization signal was seen in the photoreceptor inner segments and was unequivocally absent from the RPE (FIG. **7**E). Given that ABCR transcripts in each of these mammals, including a primate, are photoreceptor-specific, it is highly likely that the distribution of ABCR transcripts conforms to this pattern as well in the human retina.

The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

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    370                 375                 380

Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr
385                 390                 395                 400

Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser
                405                 410                 415

Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu
            420                 425                 430

Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met
        435                 440                 445

Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu
    450                 455                 460
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Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn
465                 470                 475                 480

Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn
                485                 490                 495

Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu
            500                 505                 510

Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr
        515                 520                 525

Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu
    530                 535                 540

Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr
545                 550                 555                 560

Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp
                565                 570                 575

Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly
            580                 585                 590

Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe
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Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val
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Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro
625                 630                 635                 640

Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro
                645                 650                 655

Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys
            660                 665                 670

Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn
        675                 680                 685

Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser
    690                 695                 700

Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met
705                 710                 715                 720

His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe
                725                 730                 735

Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser
            740                 745                 750

Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile
        755                 760                 765

Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp
    770                 775                 780

Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val
785                 790                 795                 800

Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly
                805                 810                 815

Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp
            820                 825                 830

Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala
        835                 840                 845

Cys Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp
    850                 855                 860

Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp
865                 870                 875                 880

Leu Ser Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys
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Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly
            900                 905                 910

Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly
        915                 920                 925

Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro
    930                 935                 940

Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala
945                 950                 955                 960

Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu
                965                 970                 975

Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg
            980                 985                 990

Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys
        995                1000                1005

Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met
   1010                1015                1020

Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu
1025                1030                1035                1040

Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn
               1045                1050                1055

Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val
           1060                1065                1070

Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro
       1075                1080                1085

Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu
   1090                1095                1100

Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Pro Thr His His Met
1105                1110                1115                1120

Asp Glu Ala Asp His Gln Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly
               1125                1130                1135

Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly
           1140                1145                1150

Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser
       1155                1160                1165

Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe
   1170                1175                1180

Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val
1185                1190                1195                1200

Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val
               1205                1210                1215

Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu
           1220                1225                1230

Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg
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Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile
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Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser
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Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn
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Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln
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Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu
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Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val
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Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln
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Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile
           1380                1385                1390

Val Ile Leu Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp
       1395                1400                1405

Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser
   1410                1415                1420

Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe
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Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly
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Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln
           1460                1465                1470

Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys
       1475                1480                1485

Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu
   1490                1495                1500

Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu
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Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys
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Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val
           1540                1545                1550

Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val
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Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly
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Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys
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Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys
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Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn
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Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser
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Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr
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Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala
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Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser
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Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu
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Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe
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Leu Trp Asp Ile Met Asn Tyr Ser Val Ser Ala Gly Leu Val Val Gly
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Ile Phe Ile Gly Phe Gln Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu
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Pro Ala Leu Val Ala Leu Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro
               1765                1770                1775

Met Met Tyr Pro Ala Ser Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr
           1780                1785                1790

Val Ala Leu Ser Cys Ala Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala
       1795                1800                1805

Ile Thr Phe Ile Leu Glu Leu Phe Asp Asn Asn Arg Thr Leu Leu Arg
   1810                1815                1820

Phe Asn Ala Val Leu Arg Lys Leu Leu Ile Val Phe Pro His Phe Cys
1825               1830                1835                1840

Leu Gly Arg Gly Leu Ile Asp Leu Ala Leu Ser Gln Ala Val Thr Asp
               1845                1850                1855

Val Tyr Ala Arg Phe Gly Glu Glu His Ser Ala Asn Pro Phe His Trp
           1860                1865                1870

Asp Leu Ile Gly Lys Asn Leu Phe Ala Met Val Val Glu Gly Val Val
       1875                1880                1885

Tyr Phe Leu Leu Thr Leu Leu Val Gln Arg His Phe Phe Leu Ser Gln
   1890                1895                1900

Trp Ile Ala Glu Pro Thr Lys Glu Pro Ile Val Asp Glu Asp Asp Asp
1905               1910                1915                1920

Val Ala Glu Glu Arg Gln Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp
               1925                1930                1935

Ile Leu Arg Leu His Glu Leu Thr Lys Ile Tyr Leu Gly Thr Ser Ser
           1940                1945                1950

Pro Ala Val Asp Arg Leu Cys Val Gly Val Arg Pro Gly Glu Cys Phe
       1955                1960                1965

Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met
   1970                1975                1980

Leu Thr Gly Asp Thr Thr Val Thr Ser Gly Asp Ala Thr Val Ala Gly
1985               1990                1995                2000

Lys Ser Ile Leu Thr Asn Ile Ser Glu Val His Gln Asn Met Gly Tyr
               2005                2010                2015

Cys Pro Gln Phe Asp Ala Ile Asp Glu Leu Leu Thr Gly Arg Glu His
           2020                2025                2030

Leu Tyr Leu Tyr Ala Arg Leu Arg Gly Val Pro Ala Glu Glu Ile Glu
       2035                2040                2045

Lys Val Ala Asn Trp Ser Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala
   2050                2055                2060

Asp Cys Leu Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser
2065               2070                2075                2080

Thr Ala Ile Ala Leu Ile Gly Cys Pro Pro Leu Val Leu Leu Asp Glu
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Pro Thr Thr Gly Met Asp Pro Gln Ala Arg Arg Met Leu Trp Asn Val
           2100                2105                2110

Ile Val Ser Ile Ile Arg Lys Gly Arg Ala Val Val Leu Thr Ser His
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Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val
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Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys
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Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp
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Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe
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His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr
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Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His
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accacactgg accaggtgtt tgtaaatttt gctaaacagc agactgaaag tcatgacctc 6660

cctctgcacc ctcgagctgc tggagccagt cgacaagccc aggac 6705

<210> SEQ ID NO 6
<211> LENGTH: 2235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr
1 5 10 15

Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro
20 25 30

Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu
35 40 45

Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala
50 55 60

Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro
65 70 75 80

Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn
85 90 95

Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
100 105 110

Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
115 120 125

Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
130 135 140

Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu
145 150 155 160

Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
165 170 175

Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala
180 185 190

His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala
195 200 205

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Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr
    210                 215                 220

Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile
225                 230                 235                 240

Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val
                245                 250                 255

Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser
            260                 265                 270

Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile
        275                 280                 285

His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met
    290                 295                 300

Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser
305                 310                 315                 320

Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser
                325                 330                 335

Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp
            340                 345                 350

Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser
        355                 360                 365

Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys
    370                 375                 380

Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr
385                 390                 395                 400

Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser
                405                 410                 415

Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu
            420                 425                 430

Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met
        435                 440                 445

Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu
    450                 455                 460

Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn
465                 470                 475                 480

Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn
                485                 490                 495

Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu
            500                 505                 510

Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr
        515                 520                 525

Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu
    530                 535                 540

Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr
545                 550                 555                 560

Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp
                565                 570                 575

Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly
            580                 585                 590

Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe
        595                 600                 605

Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val
    610                 615                 620

Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro
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625                 630                 635                 640

Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro
                645                 650                 655

Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys
            660                 665                 670

Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn
        675                 680                 685

Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser
    690                 695                 700

Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met
705                 710                 715                 720

His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe
                725                 730                 735

Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser
            740                 745                 750

Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile
        755                 760                 765

Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp
    770                 775                 780

Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val
785                 790                 795                 800

Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly
                805                 810                 815

Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp
            820                 825                 830

Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala
        835                 840                 845

Cys Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp
    850                 855                 860

Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp
865                 870                 875                 880

Leu Ser Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys
                885                 890                 895

Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly
            900                 905                 910

Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly
        915                 920                 925

Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro
    930                 935                 940

Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala
945                 950                 955                 960

Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu
                965                 970                 975

Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg
            980                 985                 990

Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys
        995                1000                1005

Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met
   1010                1015                1020

Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu
1025                1030                1035                1040

Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn
                1045                1050                1055
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Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val
            1060                1065                1070

Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro
        1075                1080                1085

Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu
    1090                1095                1100

Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Pro Thr His His Met
1105                1110                1115                1120

Asp Glu Ala Asp His Gln Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly
                1125                1130                1135

Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly
            1140                1145                1150

Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser
        1155                1160                1165

Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe
    1170                1175                1180

Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val
1185                1190                1195                1200

Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val
                1205                1210                1215

Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu
            1220                1225                1230

Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg
        1235                1240                1245

Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile
    1250                1255                1260

Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser
1265                1270                1275                1280

Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn
                1285                1290                1295

Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln
            1300                1305                1310

Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His
        1315                1320                1325

Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu
    1330                1335                1340

Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val
1345                1350                1355                1360

Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln
                1365                1370                1375

Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile
            1380                1385                1390

Val Ile Leu Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp
        1395                1400                1405

Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser
    1410                1415                1420

Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe
1425                1430                1435                1440

Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Cys Ser Thr Arg Glu
                1445                1450                1455

Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro
            1460                1465                1470
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Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr
       1475                1480                1485

Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile
   1490                1495                1500

Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly
1505                1510                1515                1520

Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu
               1525                1530                1535

Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser
           1540                1545                1550

Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu
       1555                1560                1565

Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys
   1570                1575                1580

Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile
1585                1590                1595                1600

Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile
               1605                1610                1615

Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu
           1620                1625                1630

Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val
       1635                1640                1645

Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile
   1650                1655                1660

Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val
1665                1670                1675                1680

Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn
               1685                1690                1695

Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln
           1700                1705                1710

Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu
       1715                1720                1725

Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser
   1730                1735                1740

Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala
1745                1750                1755                1760

Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu
               1765                1770                1775

Leu Phe Asp Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg
           1780                1785                1790

Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile
       1795                1800                1805

Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly
   1810                1815                1820

Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn
1825                1830                1835                1840

Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu
               1845                1850                1855

Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr
           1860                1865                1870

Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln
       1875                1880                1885

Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu
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   1890                1895                1900

Leu Thr Lys Ile Tyr Leu Gly Thr Ser Ser Pro Ala Val Asp Arg Leu
1905                1910                1915                1920

Cys Val Gly Val Arg Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn
                1925                1930                1935

Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Thr
            1940                1945                1950

Val Thr Ser Gly Asp Ala Thr Val Ala Gly Lys Ser Ile Leu Thr Asn
        1955                1960                1965

Ile Ser Glu Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala
   1970                1975                1980

Ile Asp Glu Leu Leu Thr Gly Arg Glu His Leu Tyr Leu Tyr Ala Arg
1985                1990                1995                2000

Leu Arg Gly Val Pro Ala Glu Glu Ile Glu Lys Val Ala Asn Trp Ser
                2005                2010                2015

Ile Lys Ser Leu Gly Leu Thr Val Tyr Ala Asp Cys Leu Ala Gly Thr
            2020                2025                2030

Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile
        2035                2040                2045

Gly Cys Pro Pro Leu Val Leu Leu Asp Glu Pro Thr Thr Gly Met Asp
   2050                2055                2060

Pro Gln Ala Arg Arg Met Leu Trp Asn Val Ile Val Ser Ile Ile Arg
2065                2070                2075                2080

Lys Gly Arg Ala Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu
                2085                2090                2095

Ala Leu Cys Thr Arg Leu Ala Ile Met Val Lys Gly Ala Phe Arg Cys
            2100                2105                2110

Met Gly Thr Ile Gln His Leu Lys Ser Lys Phe Gly Asp Gly Tyr Ile
        2115                2120                2125

Val Thr Met Lys Ile Lys Ser Pro Lys Asp Asp Leu Leu Pro Asp Leu
   2130                2135                2140

Asn Pro Val Glu Gln Phe Phe Gln Gly Asn Phe Pro Gly Ser Val Gln
2145                2150                2155                2160

Arg Glu Arg His Tyr Asn Met Leu Gln Phe Gln Val Ser Ser Ser Ser
                2165                2170                2175

Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser His Lys Asp Ser Leu Leu
            2180                2185                2190

Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr Leu Asp Gln Val Phe Val
        2195                2200                2205

Asn Phe Ala Lys Gln Gln Thr Glu Ser His Asp Leu Pro Leu His Pro
   2210                2215                2220

Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln Asp
2225                2230                2235


<210> SEQ ID NO 7
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 7

atcctctgac tcagcaatca ca                                              22


<210> SEQ ID NO 8
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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 8

ttgcaattac aaatgcaatg g 21

<210> SEQ ID NO 9
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 9

atccataccc ttcccactcc 20

<210> SEQ ID NO 10
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 10

gcagcagaag ataagcacac c 21

<210> SEQ ID NO 11
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser
1 5 10 15

Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn
20 25 30

Pro Ser Pro Ser Cys Arg
35

<210> SEQ ID NO 12
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 12

accctctgct aagctcagag 20

<210> SEQ ID NO 13
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 13

accccacact tccaacctg 19

<210> SEQ ID NO 14
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 14

aagtcctact gcacacatgg 20

<210> SEQ ID NO 15
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 15

acactcccac cccaagatc 19

<210> SEQ ID NO 16
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 16

ttcccaaaaa ggccaactc 19

<210> SEQ ID NO 17
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 17

cacgcacgtg tgcattcag 19

<210> SEQ ID NO 18
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 18

gctatttcct tattaatgag gc 22

<210> SEQ ID NO 19
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 19

ccaactctcc ctgttctttc 20

<210> SEQ ID NO 20
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 20

tgtttccaat cgactctggc 20

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<210> SEQ ID NO 21
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 21

ttcttgcctt tctcaggctg g 21

<210> SEQ ID NO 22
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 22

gtattcccag gttctgtgg 19

<210> SEQ ID NO 23
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 23

taccccagga atcaccttg 19

<210> SEQ ID NO 24
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 24

agcatatagg agatcagact g 21

<210> SEQ ID NO 25
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 25

tgacataagt ggggtaaatg g 21

<210> SEQ ID NO 26
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 26

gagcattggc ctcacagcag 20

<210> SEQ ID NO 27
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 27

ccccaggttt gtttcacc 18

<210> SEQ ID NO 28
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 28

agacatgtga tgtggataca c 21

<210> SEQ ID NO 29
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 29

gtgggaggtc cagggtacac 20

<210> SEQ ID NO 30
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 30

aggggcagaa aagacacac 19

<210> SEQ ID NO 31
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 31

tagcgattaa ctctttcctg g 21

<210> SEQ ID NO 32
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 32

ctcttcaggg agccttagc 19

<210> SEQ ID NO 33
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 33

ttcaagacca cttgacttgc 20

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<210> SEQ ID NO 34
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 34

tgggacagca gccttatc 18

<210> SEQ ID NO 35
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 35

ccaaatgtaa tttcccactg ac 22

<210> SEQ ID NO 36
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 36

aatgagttcc gagtcaccct g 21

<210> SEQ ID NO 37
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 37

cccattcgcg tgtcatgg 18

<210> SEQ ID NO 38
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 38

tccatctggg ctttgttctc 20

<210> SEQ ID NO 39
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 39

aatccaggca catgaacagg 20

<210> SEQ ID NO 40
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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<400> SEQUENCE: 40

aggctggtgg gagagagc 18

<210> SEQ ID NO 41
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 41

agtggacccc ctcagagg 18

<210> SEQ ID NO 42
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 42

ctgttgcatt ggataaaagg c 21

<210> SEQ ID NO 43
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 43

gatgaatgga gagggctgg 19

<210> SEQ ID NO 44
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 44

ctgcggtaag gtaggatagg g 21

<210> SEQ ID NO 45
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 45

cacaccgttt acatagaggg c 21

<210> SEQ ID NO 46
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 46

cctctcccct cctttcctg 19

<210> SEQ ID NO 47
<211> LENGTH: 19

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 47

gtcagtttcc gtaggcttc 19

<210> SEQ ID NO 48
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 48

tggggccatg taattaggc 19

<210> SEQ ID NO 49
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 49

tgggaaagag tagacagccg 20

<210> SEQ ID NO 50
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 50

actgaacctg gtgtgggg 18

<210> SEQ ID NO 51
<211> LENGTH: 19
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 51

tatctctgcc tgtgcccag 19

<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 52

gtaagatcag ctgctggaag 20

<210> SEQ ID NO 53
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 53

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gaagctctcc tgcaccaagc 20

<210> SEQ ID NO 54
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 54

aggtaccccc acaatgcc 18

<210> SEQ ID NO 55
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 55

tcattgtggt tccagtactc ag 22

<210> SEQ ID NO 56
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 56

tttttgcaac tatatagcca gg 22

<210> SEQ ID NO 57
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 57

agcctgtgtg agtagccatg 20

<210> SEQ ID NO 58
<211> LENGTH: 19
<212> TYPE: DNA
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<400> SEQUENCE: 58

gcatcagggc gaggctgtc 19

<210> SEQ ID NO 59
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 59

cccagcaata ctgggagatg 20

<210> SEQ ID NO 60
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 60

ggtaacctca cagtcttcc 19

<210> SEQ ID NO 61
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 61

gggaacgatg gctttttgc 19

<210> SEQ ID NO 62
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 62

tcccattatg aagcaatacc 20

<210> SEQ ID NO 63
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 63

ccttagactt tcgagatgg 19

<210> SEQ ID NO 64
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 64

gctaccagcc tggtatttca ttg 23

<210> SEQ ID NO 65
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 65

gttataaccc atgcctgaag 20

<210> SEQ ID NO 66
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 66

tgcacgcgca cgtgtgac 18

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<210> SEQ ID NO 67
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 67

tgaaggtccc agtgaagtgg g 21

<210> SEQ ID NO 68
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<400> SEQUENCE: 68

cagcagctat ccagtaaagg 20

<210> SEQ ID NO 69
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<400> SEQUENCE: 69

aacgcctgcc atcttgaac 19

<210> SEQ ID NO 70
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<212> TYPE: DNA
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<400> SEQUENCE: 70

gttgggcaca attcttatgc 20

<210> SEQ ID NO 71
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<212> TYPE: DNA
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<400> SEQUENCE: 71

gttgtttgga ggtcaggtac 20

<210> SEQ ID NO 72
<211> LENGTH: 21
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 72

aacatcaccc agctgttcca g 21

<210> SEQ ID NO 73
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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<400> SEQUENCE: 73

actcaggaga taccagggac 20

<210> SEQ ID NO 74
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 74

ggaagacaac aagcagtttc ac 22

<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 75

atctactgcc ctgatcatac 20

<210> SEQ ID NO 76
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 76

aagactgaga cttcagtctt c 21

<210> SEQ ID NO 77
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 77

ggtgtgcctt ttaaaagtgt gc 22

<210> SEQ ID NO 78
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 78

ttcatgtttc cctacaaaac cc 22

<210> SEQ ID NO 79
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 79

catgagagtt tctcattcat gg 22

<210> SEQ ID NO 80

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<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 80

tgtttacatg gtttttaggg cc 22

<210> SEQ ID NO 81
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 81

ttcagcagga ggagggatg 19

<210> SEQ ID NO 82
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 82

cctttccttc actgatttct gc 22

<210> SEQ ID NO 83
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 83

aatcagcact tcgcggtg 18

<210> SEQ ID NO 84
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 84

tgtaaggcct tcccaaagc 19

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 85

tggtccttca gcgcacacac 20

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 86

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catttgcag agctggcagc 20

<210> SEQ ID NO 87
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 87

cttctgtcag gagatgatcc 20

<210> SEQ ID NO 88
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 88

ggagtgcatt atatccagac g 21

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 89

cctggctctg cttgaccaac 20

<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 90

tgctgtcctg tgagagcatc 20

<210> SEQ ID NO 91
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 91

gtaaccctcc cagctttgg 19

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 92

cagttcccac ataaggcctg 20

<210> SEQ ID NO 93
<211> LENGTH: 19
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 93

cagttctgga tgccctgag 19

<210> SEQ ID NO 94
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 94

gaagagaggt cccatggaaa gg 22

<210> SEQ ID NO 95
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 95

gcttgcataa gcatatcaat tg 22

<210> SEQ ID NO 96
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 96

ctcctaaacc atcctttgct c 21

<210> SEQ ID NO 97
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 97

aggcaggcac aagagctg 18

<210> SEQ ID NO 98
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 98

cttaccctgg ggcctgac 18

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 99

ctcagagcca ccctactata g 21

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<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 100

gaagcttctc cagccctagc 20

<210> SEQ ID NO 101
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 101

tgcactctca tgaaacaggc 20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 102

gtttggggtg tttgcttgtc 20

<210> SEQ ID NO 103
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 103

acctctttcc ccaacccaga g 21

<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 104

gaagcagtaa tcagaagggc 20

<210> SEQ ID NO 105
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 105

gcctcacatt cttccatgct g 21

<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 106

tcacatccca caggcaagag 20

<210> SEQ ID NO 107
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 107

ttccaagtgt caatggagaa c 21

<210> SEQ ID NO 108
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 108

attaccttag gcccaaccac 20

<210> SEQ ID NO 109
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 109

acactgggtg ttctggacc 19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 110

gtgtagggtg gtgttttcc 19

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 111

aagcccagtg aaccagctgg 20

<210> SEQ ID NO 112
<211> LENGTH: 19
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 112

tcagctgagt gcccttcag 19

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<210> SEQ ID NO 113
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 113

aggtgagcaa gtcagtttcg g 21

<210> SEQ ID NO 114
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 114

ggtcttcgtg tgtggtcatt 20

<210> SEQ ID NO 115
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 115

ggtccagttc ttccagag 18

<210> SEQ ID NO 116
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 116

atcctctgac tcagcaatca ca 22

<210> SEQ ID NO 117
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 117

ttgcaattac aaatgcaatg g 21

<210> SEQ ID NO 118
<211> LENGTH: 2261
<212> TYPE: PRT
<213> ORGANISM: Murine sp.
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (175)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 118

Met Ala Cys Xaa Pro Gln Leu Arg Leu Leu Leu Trp Lys Asn Leu Thr
1 5 10 15

Phe Arg Arg Arg Gln Thr Cys Gln Leu Leu Leu Glu Val Ala Trp Pro

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            20                  25                  30

Leu Phe Ile Phe Leu Ile Leu Ile Ser Val Arg Leu Ser Tyr Pro Pro
         35                  40                  45

Tyr Glu Gln His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala
     50                  55                  60

Gly Thr Leu Pro Trp Val Gln Gly Ile Ile Cys Asn Ala Asn Asn Pro
 65                  70                  75                  80

Cys Phe Arg Tyr Pro Thr Pro Gly Glu Ala Pro Gly Val Val Gly Asn
                 85                  90                  95

Phe Asn Lys Ser Ile Val Ser Arg Leu Phe Ser Asp Ala Gln Arg Leu
            100                 105                 110

Leu Leu Tyr Ser Gln Arg Asp Thr Ser Ile Lys Asp Met His Lys Val
        115                 120                 125

Leu Arg Met Leu Arg Gln Ile Lys His Pro Asn Ser Asn Leu Lys Leu
    130                 135                 140

Gln Asp Phe Leu Val Asp Asn Glu Thr Phe Ser Gly Phe Leu Gln His
145                 150                 155                 160

Asn Leu Ser Leu Pro Arg Ser Thr Val Asp Ser Leu Leu Gln Xaa Asn
                165                 170                 175

Val Gly Leu Gln Lys Val Phe Leu Gln Gly Tyr Gln Leu His Leu Ala
            180                 185                 190

Ser Leu Cys Asn Gly Ser Lys Leu Glu Glu Ile Ile Gln Leu Gly Asp
        195                 200                 205

Ala Glu Val Ser Ala Leu Cys Gly Leu Pro Arg Lys Lys Leu Asp Ala
    210                 215                 220

Ala Glu Arg Val Leu Arg Tyr Asn Met Asp Ile Leu Lys Pro Val Val
225                 230                 235                 240

Thr Lys Leu Asn Ser Thr Ser His Leu Pro Thr Gln His Leu Ala Glu
                245                 250                 255

Ala Thr Thr Val Leu Leu Asp Ser Leu Gly Gly Leu Ala Gln Glu Leu
            260                 265                 270

Phe Ser Thr Lys Ser Trp Ser Asp Met Arg Gln Glu Val Met Phe Leu
        275                 280                 285

Thr Asn Val Asn Ser Ser Ser Ser Ser Thr Gln Ile Tyr Gln Ala Val
    290                 295                 300

Ser Arg Ile Val Cys Gly His Pro Glu Gly Gly Gly Leu Lys Ile Lys
305                 310                 315                 320

Ser Leu Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Leu Phe Gly Gly
                325                 330                 335

Asn Asn Thr Glu Glu Asp Val Asp Thr Phe Tyr Asp Asn Ser Thr Thr
            340                 345                 350

Pro Tyr Cys Asn Asp Leu Met Lys Asn Leu Glu Ser Ser Pro Leu Ser
        355                 360                 365

Arg Ile Ile Trp Lys Ala Leu Lys Pro Leu Leu Val Gly Lys Ile Leu
    370                 375                 380

Tyr Thr Pro Asp Thr Pro Ala Thr Arg Gln Val Met Ala Glu Val Asn
385                 390                 395                 400

Lys Thr Phe Gln Glu Leu Ala Val Phe His Asp Leu Glu Gly Met Trp
                405                 410                 415

Glu Glu Leu Ser Pro Gln Ile Trp Thr Phe Met Glu Asn Ser Gln Glu
            420                 425                 430

Met Asp Leu Val Arg Thr Leu Leu Asp Ser Arg Gly Asn Asp Gln Phe
        435                 440                 445
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Trp Glu Gln Lys Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Met
    450                 455                 460

Ala Phe Leu Ala Lys Asn Pro Glu Asp Val Gln Ser Pro Asn Gly Ser
465                 470                 475                 480

Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Gln
                485                 490                 495

Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro
            500                 505                 510

Ile Pro Thr Glu Val Arg Leu Ile Asn Lys Ser Met Glu Leu Leu Asp
        515                 520                 525

Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Asp
    530                 535                 540

Ser Val Glu Leu Pro His His Val Lys Tyr Lys Ile Arg Met Asp Ile
545                 550                 555                 560

Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro
                565                 570                 575

Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly
            580                 585                 590

Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu
        595                 600                 605

Thr Gly Ser Glu Lys Lys Thr Gly Val Tyr Val Gln Gln Met Pro Tyr
    610                 615                 620

Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met
625                 630                 635                 640

Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile
                645                 650                 655

Lys Ser Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg
            660                 665                 670

Ile Met Gly Leu Asp Asn Gly Ile Leu Trp Phe Ser Trp Phe Val Ser
        675                 680                 685

Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu
    690                 695                 700

Lys Leu Gly Asn Leu Leu Pro Tyr Ser Asp Pro Ser Val Val Phe Val
705                 710                 715                 720

Phe Leu Ser Val Phe Ala Met Val Thr Ile Leu Gln Cys Phe Leu Ile
                725                 730                 735

Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Ala Cys Gly Gly Ile
            740                 745                 750

Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala Trp Gln
        755                 760                 765

Asp Tyr Val Gly Phe Ser Ile Lys Ile Phe Ala Ser Leu Leu Ser Pro
    770                 775                 780

Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Glu Gln
785                 790                 795                 800

Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu
                805                 810                 815

Asp Gly Phe Asn Leu Thr Thr Ala Val Ser Met Met Leu Phe Asp Thr
            820                 825                 830

Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly
        835                 840                 845

Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr
    850                 855                 860
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Trp Phe Gly Glu Glu Ile Asp Glu Lys Ser His Pro Gly Ser Ser Gln
865                 870                 875                 880

Lys Gly Val Ser Glu Ile Cys Met Glu Glu Glu Pro Thr His Leu Arg
                885                 890                 895

Leu Gly Val Ser Ile Gln Asn Leu Val Lys Val Tyr Arg Asp Gly Met
            900                 905                 910

Lys Val Ala Val Asp Gly Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile
        915                 920                 925

Thr Ser Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser
    930                 935                 940

Ile Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu
945                 950                 955                 960

Gly Lys Asp Ile Arg Ser Glu Met Ser Ser Ile Arg Gln Asn Leu Gly
                965                 970                 975

Val Cys Pro Gln His Asn Val Leu Phe Asp Met Leu Thr Val Glu Glu
            980                 985                 990

His Ile Trp Phe Tyr Ala Arg Leu Lys Gly Leu Ser Glu Lys His Val
        995                1000                1005

Lys Ala Glu Met Glu Gln Met Ala Leu Asp Val Gly Leu Pro Pro Ser
   1010                1015                1020

Lys Leu Lys Ser Lys Thr Ser Gln Leu Ser Gly Gly Met Gln Arg Lys
1025                1030                1035                1040

Leu Ser Val Ala Leu Ala Phe Val Gly Gly Ser Lys Val Val Ile Leu
               1045                1050                1055

Asp Glu Pro Thr Ala Gly Val Asp Pro Tyr Ser Arg Arg Gly Ile Trp
           1060                1065                1070

Glu Leu Leu Leu Lys Tyr Arg Gln Gly Arg Thr Ile Ile Leu Ser Thr
       1075                1080                1085

His His Met Asp Glu Ala Asp Ile Leu Gly Asp Arg Ile Ala Ile Ile
   1090                1095                1100

Ser His Gly Lys Leu Cys Cys Val Gly Ser Ser Leu Phe Leu Lys Asn
1105                1110                1115                1120

Gln Leu Gly Thr Gly Tyr Tyr Leu Thr Leu Val Lys Lys Asp Val Glu
               1125                1130                1135

Ser Ser Leu Ser Ser Cys Arg Asn Ser Ser Ser Thr Val Ser Cys Leu
           1140                1145                1150

Lys Lys Glu Asp Ser Val Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly
       1155                1160                1165

Ser Asp His Glu Ser Asp Thr Leu Thr Ile Asp Val Ser Ala Ile Ser
   1170                1175                1180

Asn Leu Ile Arg Lys His Val Ser Glu Ala Arg Leu Val Glu Asp Ile
1185                1190                1195                1200

Gly His Glu Leu Thr Tyr Val Leu Pro Tyr Glu Ala Ala Lys Glu Gly
               1205                1210                1215

Ala Phe Val Glu Leu Phe His Glu Ile Asp Asp Arg Leu Ser Asp Leu
           1220                1225                1230

Gly Ile Ser Ser Tyr Gly Ile Ser Glu Thr Thr Leu Glu Glu Ile Phe
       1235                1240                1245

Leu Lys Val Ala Glu Glu Ser Gly Val Asp Ala Glu Thr Ser Asp Gly
   1250                1255                1260

Thr Leu Pro Ala Arg Arg Asn Arg Arg Ala Phe Gly Asp Lys Gln Ser
1265                1270                1275                1280

Cys Leu His Pro Phe Thr Glu Asp Asp Ala Val Asp Pro Asn Asp Ser
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             1285                1290                1295

Asp Ile Asp Pro Glu Ser Arg Glu Thr Asp Leu Leu Ser Gly Met Asp
          1300                1305                1310

Gly Lys Gly Ser Tyr Gln Leu Lys Gly Trp Lys Leu Thr Gln Gln Gln
       1315                1320                1325

Phe Val Ala Leu Leu Trp Lys Arg Leu Leu Ile Ala Arg Arg Ser Arg
   1330                1335                1340

Lys Gly Phe Phe Ala Gln Ile Val Leu Pro Ala Val Phe Val Cys Ile
1345                1350                1355                1360

Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly Lys Tyr Pro Ser
             1365                1370                1375

Leu Glu Leu Gln Pro Trp Met Tyr Asn Glu Gln Tyr Thr Phe Val Ser
          1380                1385                1390

Asn Asp Ala Pro Glu Asp Met Gly Thr Gln Glu Leu Leu Asn Ala Leu
       1395                1400                1405

Thr Lys Asp Pro Gly Phe Gly Thr Arg Cys Met Glu Gly Asn Pro Ile
   1410                1415                1420

Pro Asp Thr Pro Cys Leu Ala Gly Glu Glu Asp Trp Thr Ile Ser Pro
1425                1430                1435                1440

Val Pro Gln Ser Ile Val Asp Leu Phe Gln Asn Gly Asn Trp Thr Met
             1445                1450                1455

Lys Asn Pro Ser Pro Ala Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys
          1460                1465                1470

Met Leu Pro Val Cys Pro Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln
       1475                1480                1485

Arg Lys Gln Lys Thr Ala Asp Ile Leu Gln Asn Leu Thr Gly Arg Asn
   1490                1495                1500

Ile Ser Asp Tyr Leu Val Lys Thr Tyr Val Gln Ile Ile Ala Lys Ser
1505                1510                1515                1520

Leu Lys Asn Lys Ile Trp Val Asn Glu Phe Arg Tyr Gly Gly Phe Ser
             1525                1530                1535

Leu Gly Val Ser Asn Ser Gln Ala Leu Pro Pro Ser His Glu Val Asn
          1540                1545                1550

Asp Ala Ile Lys Gln Met Lys Lys Leu Leu Lys Leu Thr Lys Asp Thr
       1555                1560                1565

Ser Ala Asp Arg Phe Leu Ser Ser Leu Gly Arg Phe Met Ala Gly Leu
   1570                1575                1580

Asp Thr Lys Asn Asn Val Lys Val Trp Phe Asn Asn Lys Gly Trp His
1585                1590                1595                1600

Ala Ile Ser Ser Phe Leu Asn Val Ile Asn Asn Ala Ile Leu Arg Ala
             1605                1610                1615

Asn Leu Gln Lys Gly Glu Asn Pro Ser Gln Tyr Gly Ile Thr Ala Phe
          1620                1625                1630

Asn His Pro Leu Asn Leu Thr Lys Gln Gln Leu Ser Glu Val Ala Leu
       1635                1640                1645

Met Thr Thr Ser Val Asp Val Leu Val Ser Ile Cys Val Ile Phe Ala
   1650                1655                1660

Met Ser Phe Val Pro Ala Ser Phe Val Val Phe Leu Ile Gln Glu Arg
1665                1670                1675                1680

Val Ser Lys Ala Lys His Leu Gln Phe Ile Ser Gly Val Lys Pro Val
             1685                1690                1695

Ile Tyr Trp Leu Ser Asn Phe Val Trp Asp Met Cys Asn Tyr Val Val
          1700                1705                1710
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Pro Ala Thr Leu Val Ile Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser
       1715                1720                1725

Tyr Val Ser Ser Thr Asn Leu Pro Val Leu Ala Leu Leu Leu Leu Leu
   1730                1735                1740

Tyr Gly Trp Ser Ile Thr Pro Leu Met Tyr Pro Ala Ser Phe Val Phe
1745                1750                1755                1760

Lys Ile Pro Ser Thr Ala Tyr Val Val Leu Thr Ser Val Asn Leu Phe
               1765                1770                1775

Ile Gly Ile Asn Gly Ser Val Ala Thr Phe Val Leu Glu Leu Phe Thr
           1780                1785                1790

Asn Asn Lys Leu Asn Asp Ile Asn Asp Ile Leu Lys Ser Val Phe Leu
       1795                1800                1805

Ile Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Met Val Lys
   1810                1815                1820

Asn Gln Ala Met Ala Asp Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe
1825                1830                1835                1840

Val Ser Pro Leu Ser Trp Asp Leu Val Gly Arg Asn Leu Phe Ala Met
               1845                1850                1855

Ala Val Glu Gly Val Val Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr
           1860                1865                1870

Arg Phe Phe Ile Arg Pro Arg Pro Val Lys Ala Lys Leu Pro Pro Leu
       1875                1880                1885

Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp
   1890                1895                1900

Gly Gly Gly Gln Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile
1905                1910                1915                1920

Tyr Arg Arg Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Ile Gly Ile
               1925                1930                1935

Pro Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys
           1940                1945                1950

Ser Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Pro Val Thr Arg Gly
       1955                1960                1965

Asp Ala Phe Leu Asn Lys Asn Ser Ile Leu Ser Asn Ile His Glu Val
   1970                1975                1980

His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu
1985                1990                1995                2000

Leu Thr Gly Arg Glu His Val Glu Phe Phe Ala Leu Leu Arg Gly Val
               2005                2010                2015

Pro Glu Lys Glu Val Gly Lys Phe Gly Glu Trp Ala Ile Arg Lys Leu
           2020                2025                2030

Gly Leu Val Lys Tyr Gly Glu Lys Tyr Ala Ser Asn Tyr Ser Gly Gly
       2035                2040                2045

Asn Lys Arg Lys Leu Ser Thr Ala Met Ala Leu Ile Gly Gly Pro Pro
   2050                2055                2060

Val Val Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg
2065                2070                2075                2080

Arg Phe Leu Trp Asn Cys Ala Leu Ser Ile Val Lys Glu Gly Arg Ser
               2085                2090                2095

Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr
           2100                2105                2110

Arg Met Ala Ile Met Val Asn Gly Arg Phe Arg Cys Leu Gly Ser Val
       2115                2120                2125
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Gln His Leu Lys Asn Arg Phe Gly Asp Gly Tyr Thr Ile Val Val Arg
2130 2135 2140

Ile Ala Gly Ser Asn Pro Asp Leu Lys Pro Val Gln Glu Phe Phe Gly
2145 2150 2155 2160

Leu Ala Phe Pro Gly Ser Val Leu Lys Glu Lys His Arg Asn Met Leu
2165 2170 2175

Gln Tyr Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser
2180 2185 2190

Ile Leu Ser Gln Ser Lys Lys Arg Leu His Ile Glu Asp Tyr Ser Val
2195 2200 2205

Ser Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Asp Gln
2210 2215 2220

Ser Asp Asp Asp His Leu Lys Asp Leu Ser Leu His Lys Asn Gln Thr
2225 2230 2235 2240

Val Val Asp Val Ala Val Leu Thr Ser Phe Leu Gln Asp Glu Lys Val
2245 2250 2255

Lys Glu Ser Tyr Val
2260

<210> SEQ ID NO 119
<211> LENGTH: 1472
<212> TYPE: PRT
<213> ORGANISM: Murine sp.
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (250)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (640)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (804)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 119

Gln Ala Cys Ala Met Glu Ser Arg His Phe Glu Glu Thr Arg Gly Met
1 5 10 15

Glu Glu Glu Pro Thr His Leu Pro Leu Val Val Cys Val Asp Lys Leu
20 25 30

Thr Lys Val Tyr Lys Asn Asp Lys Lys Leu Ala Leu Asn Lys Leu Ser
35 40 45

Leu Asn Leu Tyr Glu Asn Gln Val Val Ser Phe Leu Gly His Asn Gly
50 55 60

Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly Leu Phe Pro Pro
65 70 75 80

Thr Ser Gly Ser Ala Thr Ile Tyr Gly His Asp Ile Arg Thr Glu Met
85 90 95

Asp Glu Ile Arg Lys Asn Leu Gly Met Cys Pro Gln His Asn Val Leu
100 105 110

Phe Asp Arg Leu Thr Val Glu Glu His Leu Trp Phe Tyr Ser Arg Leu
115 120 125

Lys Ser Met Ala Gln Glu Glu Ile Arg Lys Glu Thr Asp Lys Met Ile
130 135 140

Glu Asp Leu Glu Leu Ser Asn Lys Arg His Ser Leu Val Gln Thr Leu
145 150 155 160

Ser Gly Gly Met Lys Arg Lys Leu Ser Val Ala Ile Ala Phe Val Gly
165 170 175

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Gly Ser Arg Ala Ile Ile Leu Asp Glu Pro Thr Ala Gly Val Asp Pro
            180                 185                 190

Tyr Ala Arg Arg Ala Ile Trp Asp Leu Ile Leu Lys Tyr Lys Pro Gly
        195                 200                 205

Arg Thr Ile Leu Leu Ser Thr His His Met Asp Glu Ala Asp Leu Leu
    210                 215                 220

Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu Lys Cys Cys Gly
225                 230                 235                 240

Ser Pro Leu Phe Leu Lys Gly Ala Tyr Xaa Asp Gly Tyr Arg Leu Thr
                245                 250                 255

Leu Val Lys Gln Pro Ala Glu Pro Gly Thr Ser Gln Glu Pro Gly Leu
            260                 265                 270

Ala Ser Ser Pro Ser Gly Cys Pro Arg Leu Ser Ser Cys Ser Glu Pro
        275                 280                 285

Gln Val Ser Gln Phe Ile Arg Lys His Val Ala Ser Ser Leu Leu Val
    290                 295                 300

Ser Asp Thr Ser Thr Glu Leu Ser Tyr Ile Leu Pro Ser Glu Ala Val
305                 310                 315                 320

Lys Lys Gly Ala Phe Glu Arg Leu Phe Gln Gln Leu Glu His Ser Leu
                325                 330                 335

Asp Ala Leu His Leu Ser Ser Phe Gly Leu Met Asp Thr Thr Leu Glu
            340                 345                 350

Glu Val Phe Leu Lys Val Ser Glu Glu Asp Gln Ser Leu Glu Asn Ser
        355                 360                 365

Glu Ala Asp Val Lys Glu Ser Arg Lys Asp Val Leu Pro Gly Ala Glu
    370                 375                 380

Gly Leu Thr Ala Val Gly Gly Gln Ala Gly Asn Leu Ala Arg Cys Ser
385                 390                 395                 400

Glu Leu Ala Gln Ser Gln Ala Ser Leu Gln Ser Ala Ser Ser Val Gly
                405                 410                 415

Ser Ala Arg Gly Glu Glu Gly Thr Gly Tyr Ser Asp Gly Tyr Gly Asp
            420                 425                 430

Tyr Arg Pro Leu Phe Asp Asn Leu Gln Asp Pro Asp Asn Val Ser Leu
        435                 440                 445

Gln Glu Ala Glu Met Glu Ala Leu Ala Gln Val Gly Gln Gly Ser Arg
    450                 455                 460

Lys Leu Glu Gly Trp Trp Leu Lys Met Arg Gln Phe His Gly Leu Leu
465                 470                 475                 480

Val Lys Arg Phe His Cys Ala Arg Arg Asn Ser Lys Ala Leu Cys Ser
                485                 490                 495

Gln Ile Leu Leu Pro Ala Phe Phe Val Cys Val Ala Met Thr Val Ala
            500                 505                 510

Leu Ser Val Pro Glu Ile Gly Asp Leu Pro Pro Leu Val Leu Ser Pro
        515                 520                 525

Ser Gln Tyr His Asn Tyr Thr Gln Pro Arg Gly Asn Phe Ile Pro Tyr
    530                 535                 540

Ala Asn Glu Glu Arg Gln Glu Tyr Arg Leu Arg Leu Ser Pro Asp Ala
545                 550                 555                 560

Ser Pro Gln Gln Leu Val Ser Thr Phe Arg Leu Pro Ser Gly Val Gly
                565                 570                 575

Ala Thr Cys Val Leu Lys Ser Pro Ala Asn Gly Ser Leu Gly Pro Met
            580                 585                 590
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Leu Asn Leu Ser Ser Gly Glu Ser Arg Leu Leu Ala Ala Arg Phe Phe
        595                 600                 605

Asp Ser Met Cys Leu Glu Ser Phe Thr Gln Gly Leu Pro Leu Ser Asn
    610                 615                 620

Phe Val Pro Pro Pro Pro Ser Pro Ala Pro Ser Asp Ser Pro Val Xaa
625                 630                 635                 640

Pro Asp Glu Asp Ser Leu Gln Ala Trp Asn Met Ser Leu Pro Pro Thr
                645                 650                 655

Ala Gly Pro Glu Thr Trp Thr Ser Ala Pro Ser Leu Pro Arg Leu Val
            660                 665                 670

His Glu Pro Val Arg Cys Thr Cys Ser Ala Gln Gly Thr Gly Phe Ser
        675                 680                 685

Cys Pro Ser Ser Val Gly Gly His Pro Pro Gln Met Arg Val Val Thr
    690                 695                 700

Gly Asp Ile Leu Thr Asp Ile Thr Gly His Asn Val Ser Glu Tyr Leu
705                 710                 715                 720

Leu Phe Thr Ser Asp Arg Phe Arg Leu His Arg Tyr Gly Ala Ile Thr
                725                 730                 735

Phe Gly Asn Val Gln Lys Ser Ile Pro Ala Ser Phe Gly Ala Arg Val
            740                 745                 750

Pro Pro Met Val Arg Lys Ile Ala Val Arg Arg Val Ala Gln Val Leu
        755                 760                 765

Tyr Asn Asn Lys Gly Tyr His Ser Met Pro Thr Tyr Leu Asn Ser Leu
    770                 775                 780

Asn Asn Ala Ile Leu Arg Ala Asn Leu Pro Lys Ser Lys Gly Asn Pro
785                 790                 795                 800

Ala Ala Tyr Xaa Ile Thr Val Thr Asn His Pro Met Asn Lys Thr Ser
                805                 810                 815

Ala Ser Leu Ser Leu Asp Tyr Leu Leu Gln Gly Thr Asp Val Val Ile
            820                 825                 830

Ala Ile Phe Ile Ile Val Ala Met Ser Phe Val Pro Ala Ser Phe Val
        835                 840                 845

Val Phe Leu Val Ala Glu Lys Ser Thr Lys Ala Lys His Leu Gln Phe
    850                 855                 860

Val Ser Gly Cys Asn Pro Val Ile Tyr Trp Leu Ala Asn Tyr Val Trp
865                 870                 875                 880

Asp Met Leu Asn Tyr Leu Val Pro Ala Thr Cys Cys Val Ile Ile Leu
                885                 890                 895

Phe Val Phe Asp Leu Pro Ala Tyr Thr Ser Pro Thr Asn Phe Pro Ala
            900                 905                 910

Val Leu Ser Leu Phe Leu Leu Tyr Gly Trp Ser Ile Thr Pro Ile Met
        915                 920                 925

Tyr Pro Ala Ser Phe Trp Phe Glu Val Pro Ser Ser Ala Tyr Val Phe
    930                 935                 940

Leu Ile Val Ile Asn Leu Phe Ile Gly Ile Thr Ala Thr Val Ala Thr
945                 950                 955                 960

Phe Leu Leu Gln Leu Phe Glu His Asp Lys Asp Leu Lys Val Val Asn
                965                 970                 975

Ser Tyr Leu Lys Ser Cys Phe Leu Ile Phe Pro Asn Tyr Asn Leu Gly
            980                 985                 990

His Gly Leu Met Glu Met Ala Tyr Asn Glu Tyr Ile Asn Glu Tyr Tyr
        995                1000                1005

Ala Lys Ile Gly Gln Phe Asp Lys Met Lys Ser Pro Phe Glu Trp Asp
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   1010                1015                1020

Ile Val Thr Arg Gly Leu Val Ala Met Thr Val Glu Gly Phe Val Gly
1025                1030                1035                1040

Phe Phe Leu Thr Ile Met Cys Gln Tyr Asn Phe Leu Arg Gln Pro Gln
                1045                1050                1055

Arg Leu Pro Val Ser Thr Lys Pro Val Glu Asp Asp Val Asp Val Ala
            1060                1065                1070

Ser Glu Arg Gln Arg Val Leu Arg Gly Asp Ala Asp Asn Asp Met Val
        1075                1080                1085

Lys Ile Glu Asn Leu Thr Lys Val Tyr Lys Ser Arg Lys Ile Gly Arg
    1090                1095                1100

Ile Leu Ala Val Asp Arg Leu Cys Leu Gly Val Cys Val Pro Gly Glu
1105                1110                1115                1120

Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser Thr Phe
                1125                1130                1135

Lys Met Leu Thr Gly Asp Glu Ser Thr Thr Gly Gly Glu Ala Phe Val
            1140                1145                1150

Asn Gly His Ser Val Leu Lys Asp Leu Leu Gln Val Gln Gln Ser Leu
        1155                1160                1165

Gly Tyr Cys Pro Gln Phe Asp Val Pro Val Asp Glu Leu Thr Ala Arg
    1170                1175                1180

Glu His Leu Gln Leu Tyr Thr Arg Leu Arg Cys Ile Pro Trp Lys Asp
1185                1190                1195                1200

Glu Ala Gln Val Val Lys Trp Ala Leu Glu Lys Leu Glu Leu Thr Lys
                1205                1210                1215

Tyr Ala Asp Lys Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys
            1220                1225                1230

Leu Ser Thr Ala Ile Ala Leu Ile Gly Tyr Pro Ala Phe Ile Phe Leu
        1235                1240                1245

Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe Leu Trp
    1250                1255                1260

Asn Leu Ile Leu Asp Leu Ile Lys Thr Gly Arg Ser Val Val Leu Thr
1265                1270                1275                1280

Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile
                1285                1290                1295

Met Val Asn Gly Arg Leu His Cys Leu Gly Ser Ile Gln His Leu Lys
            1300                1305                1310

Asn Arg Phe Gly Asp Gly Tyr Met Ile Thr Val Arg Thr Lys Ser Ser
        1315                1320                1325

Gln Asn Val Lys Asp Val Val Arg Phe Phe Asn Arg Asn Phe Pro Glu
    1330                1335                1340

Ala His Ala Gln Gly Lys Thr Pro Tyr Lys Val Gln Tyr Gln Leu Lys
1345                1350                1355                1360

Ser Glu His Ile Ser Leu Ala Gln Val Phe Ser Lys Met Glu Gln Val
                1365                1370                1375

Val Gly Val Leu Gly Ile Glu Asp Tyr Ser Val Ser Gln Thr Thr Leu
            1380                1385                1390

Asp Asn Val Phe Val Asn Phe Ala Lys Lys Gln Ser Asp Asn Val Glu
        1395                1400                1405

Gln Gln Glu Ala Glu Pro Ser Ser Leu Pro Ser Pro Leu Gly Leu Leu
    1410                1415                1420

Ser Leu Leu Arg Pro Arg Pro Ala Pro Thr Glu Leu Arg Ala Leu Val
1425                1430                1435                1440
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Ala Asp Glu Pro Glu Asp Leu Asp Thr Glu Asp Glu Gly Leu Ile Ser
               1445                1450                1455

Phe Glu Glu Glu Arg Ala Gln Leu Ser Phe Asn Thr Asp Thr Leu Cys
           1460                1465                1470


<210> SEQ ID NO 120
<211> LENGTH: 1704
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr
  1               5                  10                  15

Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro
             20                  25                  30

Leu Leu Phe Ser Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser
         35                  40                  45

Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu
     50                  55                  60

Leu Pro Leu Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu
 65                  70                  75                  80

Ala Tyr Ile Pro Ser His Ser Asp Ala Ala Lys Thr Val Thr Glu Thr
                 85                  90                  95

Val Arg Arg Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser
            100                 105                 110

Glu Lys Asp Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser
        115                 120                 125

Val Leu Ala Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu
    130                 135                 140

Pro Leu Pro Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg
145                 150                 155                 160

Arg Asn Tyr Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr
                165                 170                 175

Glu Gly Trp His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly
            180                 185                 190

Pro Arg Glu Pro Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg
        195                 200                 205

Glu Gly Phe Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu
    210                 215                 220

Tyr His Ala Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val
225                 230                 235                 240

Thr Ile Lys Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu
                245                 250                 255

Val Ala Ile Gln Tyr Gln Leu Pro Leu Leu Leu Leu Leu Ser Phe Thr
            260                 265                 270

Tyr Thr Ala Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg
        275                 280                 285

Arg Leu Lys Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His
    290                 295                 300

Trp Ser Ala Trp Phe Leu Leu Phe Phe Leu Phe Leu Leu Ile Ala Ala
305                 310                 315                 320

Ser Phe Met Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala
                325                 330                 335

Val Leu Ser Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys
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            340                 345                 350

Phe Ala Ile Ser Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe
        355                 360                 365

Ser Lys Ala Asn Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe
    370                 375                 380

Thr Tyr Ile Pro Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr
385                 390                 395                 400

Leu Ser Gln Lys Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala
                405                 410                 415

Met Gly Ala Gln Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile
            420                 425                 430

Gln Trp Arg Asp Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys
        435                 440                 445

Phe Gly Gln Val Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly
    450                 455                 460

Leu Val Thr Trp Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val
465                 470                 475                 480

Pro Gln Pro Trp Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys
                485                 490                 495

Pro Arg Ala Val Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys
            500                 505                 510

Ala Leu Arg Asn Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala
        515                 520                 525

Gly Ile Lys Ile Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys
    530                 535                 540

Asp Arg Ala Ala Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln
545                 550                 555                 560

Ile Thr Val Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu
                565                 570                 575

Ser Met Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile
            580                 585                 590

Ser Gly Tyr Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu
        595                 600                 605

Gly Leu Cys Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala
    610                 615                 620

Glu His Leu Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys
625                 630                 635                 640

Cys Pro Glu Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp
                645                 650                 655

Lys Trp Asn Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys
            660                 665                 670

Leu Ser Ile Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu
        675                 680                 685

Asp Glu Pro Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp
    690                 695                 700

Asp Leu Leu Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr
705                 710                 715                 720

His Phe Met Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met
                725                 730                 735

Ala Lys Gly Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln
            740                 745                 750

Lys Tyr Gly Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys
        755                 760                 765
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Asn Pro Glu Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala
    770                 775                 780

Thr Leu Glu Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg
785                 790                 795                 800

Glu Ser Thr His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys
                805                 810                 815

Gln Lys Glu Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met
            820                 825                 830

Glu Glu Val Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp
        835                 840                 845

Ile Gln Ala Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg
    850                 855                 860

Ala Ser Asp Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro
865                 870                 875                 880

Ser Asp Gly Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys
                885                 890                 895

Leu Asn Thr Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe
            900                 905                 910

Leu Lys Lys Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala
        915                 920                 925

Gln Val Leu Val Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile
    930                 935                 940

Asn Tyr Ser Ser Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu
945                 950                 955                 960

Gly Glu Tyr Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser
                965                 970                 975

Gln Leu Gly Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala
            980                 985                 990

Glu Gly Gln Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu
        995                1000                1005

Ile Phe Arg Ala Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys Leu
   1010                1015                1020

Val Ala Ala Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala
1025                1030                1035                1040

Leu Phe Asn Asn Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val
                1045                1050                1055

Val Asp Asn Leu Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile
            1060                1065                1070

Val Val Ser Asn Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys
        1075                1080                1085

Asp Gln Phe Asn Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu
   1090                1095                1100

Leu Phe Ala Met Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val
1105                1110                1115                1120

Ser Glu Arg Ala Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val
                1125                1130                1135

His Val Ala Ser Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser
            1140                1145                1150

Phe Leu Ile Pro Ser Leu Leu Leu Leu Val Val Phe Lys Ala Phe Asp
        1155                1160                1165

Val Arg Ala Phe Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu
   1170                1175                1180
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Leu Leu Leu Tyr Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn
1185                1190                1195                1200

Phe Phe Phe Leu Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe
                1205                1210                1215

Asn Ile Leu Ser Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg
            1220                1225                1230

Ile Pro Ala Val Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val
        1235                1240                1245

Phe Leu Val Leu Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe
    1250                1255                1260

Tyr Glu Asn Tyr Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala
1265                1270                1275                1280

Ala His Tyr Cys Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr
                1285                1290                1295

Ala Trp Ser Ala Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala
            1300                1305                1310

Ser Gly Cys Ala Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu
        1315                1320                1325

Leu Gln Arg Leu Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Arg Thr
    1330                1335                1340

Leu Thr Glu Leu Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp
1345                1350                1355                1360

Val Ala Asp Glu Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu
                1365                1370                1375

Leu His Thr Pro Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln
            1380                1385                1390

Arg Val Pro Leu Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys
        1395                1400                1405

Gly Glu Cys Phe Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr
    1410                1415                1420

Thr Phe Lys Met Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala
1425                1430                1435                1440

Phe Val Gly Gly His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln
                1445                1450                1455

Arg Ile Gly Tyr Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr
            1460                1465                1470

Gly Arg Glu Met Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu
        1475                1480                1485

Arg His Ile Gly Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu
    1490                1495                1500

Glu Pro His Ala Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys
1505                1510                1515                1520

Arg Lys Leu Ser Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile
                1525                1530                1535

Phe Leu Asp Glu Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu
            1540                1545                1550

Leu Trp Asp Thr Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile
        1555                1560                1565

Ile Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu
    1570                1575                1580

Ala Ile Met Val Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His
1585                1590                1595                1600

Leu Lys Ser Lys Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln
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             1605                1610                1615

Ser Glu Gly Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp
          1620                1625                1630

Leu Thr Phe Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val
       1635                1640                1645

His Tyr His Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly
   1650                1655                1660

Ile Leu Glu Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val
1665                1670                1675                1680

Ser Gln Ile Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln
             1685                1690                1695

Pro Pro Thr Ala Glu Glu Gly Arg
          1700
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What is claimed is:

1. A purified nucleic acid molecule comprising a nucleic acid sequence encoding a retina-specific ATP-binding cassette transporter comprising the amino acid sequence of SEQ ID NO:3 except wherein said amino acid sequence comprises the mutation.

2. An expression vector comprising the nucleic acid molecule of claim **1**.

3. An isolated host cell comprising the expression vector of claim **2**.

4. A cell culture comprising at least one cell comprising the expression vector of claim **2**.

5. A composition comprising an effective amount of the nucleic acid molecule of claim **1** and a pharmaceutically acceptable carrier.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,141,420 B2
APPLICATION NO. : 10/340097
DATED : November 28, 2006
INVENTOR(S) : Rando Allikmets et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page,
Item (56), **References Cited**:
OTHER PUBLICATIONS
Page 2, "Allikmets, R., et al," reference, delete "eurkaryotic" and insert -- eukaryotic --
Page 2, "Cline, M.J.," reference, delete "69-62," and insert -- 69-92. --.
Page 3, "Stone, E.M., et al.," reference, delete "Stagardt-Like" and insert
-- Stargardt-Like --.
Page 3, "Gerber, S., et al.," reference, delete "Statrgardt" and insert -- Stargardt --.

Column 10,
Line 6, delete "ANABCR" and insert -- An ABCR --.

Column 16,
Line 18, delete "maybe" and insert -- may be --.
Line 21, after "may" delete "be",
Line 47, delete "^{32}p," and insert -- ^{32}P, --.

Column 21,
Line 57, delete "that[a]" and insert -- that [a] --.

Column 22,
Line 12, delete "Hofinann," and insert -- Hofmann, --.
Line 16, delete "CDNA" and insert -- cDNA --.

Column 23,
Line 1, delete "(Glavč" and insert -- (Glavač --.

Column 27,
Lines 13-14, delete "imrnmunocytochemistry" and insert -- immunocytochemistry --.
Line 14, delete "findus" and insert -- fundus --.

Column 28,
Line 8, delete "aclinical" and insert -- a clinical --.

Column 29,
Line 18, delete "Domer," and insert -- Domer, --.
Line 28, delete "RCC1" and insert -- RCC1 --.

UNITED STATES PATENT AND TRADEMARK OFFICE

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PATENT NO. : 7,141,420 B2
APPLICATION NO. : 10/340097
DATED : November 28, 2006
INVENTOR(S) : Rando Allikmets et al.

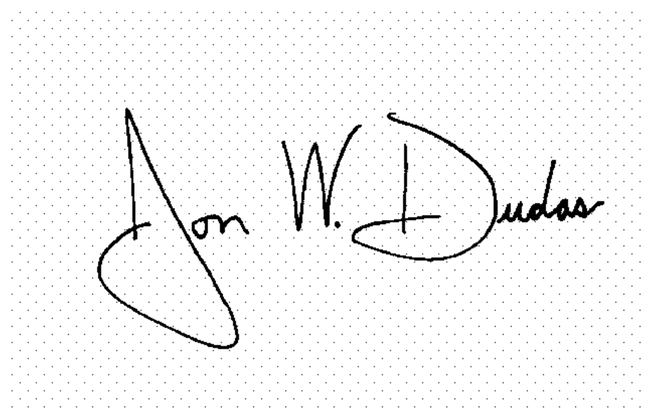
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 30,
Line 39, delete "Bems," and insert -- Berns, --.
Line 41, delete "mdr2" and insert -- mdr2--.

Column 133,
Line 26, delete "mutation." and insert -- mutation A1028V. --.

Signed and Sealed this

Twentieth Day of November, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office